DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

Centers for Disease Control and Prevention

42 CFR Part 493

[CMS–2226–F]

RIN 0938–AK24

Medicare, Medicaid, and CLIA Programs; Laboratory Requirements Relating to Quality Systems and Certain Personnel Qualifications

AGENCY: Centers for Disease Control and Prevention (CDC) and Centers for Medicare & Medicaid Services (CMS), HHS.

ACTION: Final rule.

SUMMARY: This final rule revises and responds to comments on certain laboratory requirements issued pursuant to the Clinical Laboratory Improvement Amendments of 1988 (CLIA), Pub. L. 100–578. Specifically, this final rule sets forth requirements for certain quality control (QC) provisions and personnel qualifications; consolidates and reorganizes the requirements for patient test management, QC, and quality assurance; and changes the consensus required for grading proficiency testing challenges.

To ensure a smooth transition to the new provisions for directors of high complexity testing who are not board certified (but who have doctoral degrees), we will not be holding facilities out of compliance with the provisions of the rule concerning directors who are not board certified until the effective date of this new rule, to the extent the facilities are otherwise in compliance with the requirements for laboratory directors.

EFFECTIVE DATES: This final rule is effective on April 24, 2003, except § 493.1443(b)(3) is effective on February 24, 2003.

Compliance Dates: To ensure a clear transition from the board certification provisions of the former rule at 42 CFR 493.1443(b)(2) that have a compliance date of December 31, 2002 (as set forth in 65 FR 82941), we will not be holding facilities out of compliance with the former rule until the effective date of the parallel provisions of this new rule to the extent that facilities are otherwise in compliance with the regulations for laboratory directors.

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I. Background

On February 28, 1992, we published a final rule with comment period in the **Federal Register** (57 FR 7002) that set forth the requirements for laboratories that are subject to the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

Under the provisions of the sentence following section 1861(s)(15) through 1861(s)(17) of the Social Security Act, (the Act) any laboratory that wants to be paid for services furnished to Medicare beneficiaries must meet the requirements of section 353 of the Public Health Services Act. Subject to specified exceptions, all laboratories, regardless of whether they receive payment from the Medicare or Medicaid programs must have a current and valid CLIA certificate to test human specimens. The February 28, 1992 final rule with comment period established uniform requirements based on the complexity of testing performed by laboratories regardless of the laboratory's location, size, or type. In the interest of public health, we included requirements in the February 28, 1992 final rule with comment period to ensure the quality of laboratory services.

We recognized that it would take time and resources for laboratories to understand and to implement the new requirements contained in the February 28, 1992 final rule with comment period. This final rule completes the phase-in of certain requirements where the comments supported taking this action.

The phased-in provision included quality control (QC) requirements applicable to moderate complexity tests and the date by which an individual with a doctorial degree must possess board certification to qualify as a director of a laboratory that performs high complexity testing.

During the phase-in, the Food and Drug Administration (FDA) was to establish a process to review and clear manufacturers' QC instructions for CLIA QC purposes. Because the CLIA program is user fee funded, we decided it would be prudent to wait until the phase-in period ended before implementing the FDA QC review. This afforded us the survey experience necessary to determine whether an additional FDA review process beyond that already in place as part of the premarket review would be of benefit to laboratories. We realized through our experience inspecting laboratories that an additional FDA review would not be of such benefit. We decided to remove this prospective provision. Therefore, we are removing all references to the FDA CLIA QC clearance process that was not implemented.

The phase-in effective dates contained in the February 28, 1992 final rule with comment period were further extended in the final rules with comment period published on December 6, 1994 in the **Federal Register** (59 FR 62606), May 12, 1997 in the **Federal Register** (62 FR 25855), October 14, 1998 in the **Federal Register** (63 FR 55031), and December 29, 2000 in the **Federal Register** (65 FR 82941).

The extensions allowed previously unregulated laboratories time to understand and implement these requirements. The extensions also provided the Department of Health and Human Services (HHS) additional time to issue revised QC requirements, review board certification program requests for approval, and ensure that laboratory directors with a doctoral degree had sufficient time to successfully complete the requirements for board certification.

On December 28, 2001, we published a proposed rule in the **Federal Register** (66 FR 67163) seeking comments on provisions to revise and expand the qualification requirements by which an individual with a doctoral degree in a chemical, physical, biological, or clinical laboratory science from an accredited institution may qualify to serve as a director of a laboratory performing high complexity testing. The

three proposed alternative qualification pathways were as follows:

- On or after January 1, 2003, be certified and continue to be certified by a board approved by HHS.
- Before January 1, 2003, must have served or be serving as a director of a laboratory performing high complexity testing and must have at least 2 years of laboratory training or experience, or both; and 2 years experience directing or supervising high complexity testing.
- Have at least 6 years of laboratory training or experience, or both, including 2 years of experience directing or supervising high complexity testing.

In this final rule, effective April 24, 2003, all laboratories must meet and follow the QC requirements. In addition, we are setting forth qualification requirements for an individual with a doctoral degree to serve as a director of a laboratory performing high complexity testing. Effective February 24, 2003, an individual with a doctoral degree may qualify to serve as a director of a laboratory that performs high complexity testing if he or she is certified and continues to be certified by a board approved by HHS; or before the effective date of this rule, has served or is serving as a director of a laboratory performing high complexity testing and has acquired at least 2 years of laboratory training or experience, or both, and 2 years of experience directing or supervising high complexity testing.

The qualification requirements for high complexity laboratory directors that are contained in this final rule will become effective February 24, 2003. To ensure a smooth transition to these new provisions, we will not be holding facilities out of compliance with the Board certified regulations of the former rule until the effective date of this new rule, to the extent the facilities are otherwise in compliance with the regulations for laboratory directors.

In addition, we are addressing the comments received in response to the February 28, 1992 final rule with comment period concerning part 493 of title 42 of the Code of Federal Regulations (CFR), subparts I, J, K, M, and P; comments received in response to the date-extension rules for certain provisions of subparts K and M; and comments to the December 28, 2001 proposed rule regarding qualification requirements for directors of laboratories performing high complexity testing.

II. Highlights and Organization of Final Rule

This regulation contains revisions to part 493 of title 42 of the CFR. We have renamed, reorganized, and consolidated similar requirements into one section, deleted duplicate requirements, and reworded numerous requirements to maintain and/or clarify their original intent, making the revised regulation easier to read and understand. In addition to specific changes to subparts I, J, K, M, and P, applicable technical and conforming changes were also made to other subparts.

The organization of this regulation now reflects the flow of a patient specimen through the laboratory, that is, from receipt of the specimen with the test request through test performance and test result reporting. In addition, this final rule more accurately describes the testing requirements and laboratory assessment activities.

In this final rule, the former Subpart I—Proficiency Testing Programs for Tests of Moderate Complexity (Including the Subcategory), High Complexity, or Any Combination of These Tests has been renamed Proficiency Testing Programs for Nonwaived Testing. In addition, in each specialty and subspecialty area of the subpart, we are restoring the requirement for the 80 percent agreement used by proficiency testing programs prior to the February 28, 1992 final rule with comment period.

The requirements formerly in Subpart J—Patient Test Management for Moderate Complexity (Including the Subcategory), High Complexity, or Any Combination of These Tests; Subpart K—Quality Control for Tests of Moderate Complexity (Including the Subcategory), High Complexity, or Any Combination of These Tests; and Subpart P—Quality Assurance for Moderate Complexity (Including the Subcategory) or High Complexity Testing, or Any Combination of These Tests, are consolidated and reorganized into a new Subpart J—Facility Administration for Nonwaived Testing, and Subpart K—Quality Systems for Nonwaived Testing.

As revised by this issuance, subpart J consolidates and clarifies the facility administration requirements for laboratories performing nonwaived testing. These include requirements for facility space, utilities and safety, transfusion services, and record and specimen retention. Also, subpart J now specifies that laboratories must comply with Federal, State, and local laboratory requirements. This will allow CMS to support a Federal, State, or local government that seeks to protect the public from actions it finds would be detrimental to public health. In addition, the requirements formerly at § 493.1111 (now at § 493.1242(c)) have been revised to allow CLIA-certified laboratories to refer specimens to laboratories operated under the Veterans Administration (VA), the Department of Defense (DOD), and CLIA-exempt laboratories within a State whose licensure program has been granted approval under subpart E.

Requirements pertaining to the total testing process (preanalytic, analytic, and postanalytic) are now in subpart K. Specifically, subpart K has been revised to eliminate the QC requirements formerly at § 493.1202 and provisions pertaining to the FDA review and approval of manufacturers' test system QC for CLIA purposes as specified at § 493.1203 in the February 28, 1992 final rule with comment period. Also, subpart K is now structured to correlate with the movement of a specimen through the laboratory from acquisition to examination or testing, and reporting of results. The requirements were not substantively changed to correspond to the testing process, but we did eliminate redundant requirements and revise others for clarification.

In addition, subpart K now incorporates the requirements formerly in Subpart P—Quality Assurance; Moderate Complexity (Including the Subcategory) or High Complexity Testing, or Any Combination of These Tests. These requirements are now located under the appropriate sections in subpart K, that is, General Laboratory Systems, Preanalytic Systems, Analytic Systems, and Postanalytic Systems. We listed the quality assurance (renamed quality assessment (QA) to more clearly reflect the activities performed) activities for each phase of testing. For example, QA requirements for preanalytic activities, such as monitoring the medical necessity and completeness of test request information solicited and obtained by the laboratory, now appear at the end of the preanalytic section of subpart K under § 493.1249. We believe that integrating the QA requirements into the various phases of the testing process enhances the understanding of the vital and important role QA plays in ensuring that quality services are provided by the laboratory throughout the entire testing process. To further emphasize and clarify the essential components of a comprehensive QA program, we are reiterating in each assessment section the laboratory's responsibility to: (1) Establish and follow written polices and procedures for an ongoing mechanism to monitor and assess each of its activities; (2) take corrective actions, as necessary, based on these assessments; (3) review the effectiveness of the assessments and corrective actions

taken; (4) revise policies and procedures, as necessary, to prevent recurrences of problems; (5) discuss the assessment activities and findings with the appropriate staff; and (6) document all assessment activities. To ensure the clarity of this final rule, many of the QA requirements from the former subpart P had to be rewritten.

To conform with the names of the new subparts I, J, and K, the former Subpart M—Personnel for Moderate Complexity (Including the Subcategory) and High Complexity Testing has been renamed Personnel for Nonwaived Testing. In subpart M, we are finalizing the qualification requirements for directors of laboratories performing high complexity testing at § 493.1443(b)(3). In addition, we are revising § 493.1443(b)(3)(i) by removing the reference to specific boards approved by HHS. All HHS-approved boards are listed on the Internet at *http://cms.hhs.gov/clia/dirc/con.asp.* HHS-approved boards will also be listed in Appendix C of the State Operations Manual (CMS Pub. 7), subpart M. This change will allow greater flexibility to update the list of HHS-approved boards. Also, we are announcing two new HHS-approved boards; the National Registry for Clinical Chemistry at the doctoral level and the American Board of Forensic Toxicology.

To clarify these changes, we have provided a distribution table, which contains a detailed list of sections that have been removed or redesignated.

III. Distribution Table

The following crosswalk table enables the reader to easily locate where the requirements from the former rule have been relocated. It lists the former section titles along with the section titles as they appear in this final rule. In addition, the reorganized regulation now follows the path of patient specimens as they proceed through the clinical laboratory. This organizational structure was adopted at the recommendation of the Clinical Laboratory Improvement Advisory Committee to assist laboratories in better understanding the basic CLIA requirements.

TABLE.—CROSSWALK

Former requirements and former sections (part 493, subparts J, K, M, and P)	Requirements in this final rule (part 493, subparts J, K, and M)	Sections in this final rule
Patient test management; moderate complexity (including the subcategory), or high complexity testing, or any combination of these tests:		
§ 493.1101—Introductory text	Specimen identification and integrity	§§ 493.1232;
	Preanalytic systems	493.1240;
	Postanalytic systems	493.1290
Procedures for specimen submission and handling:		
§ 493.1103(a)	Specimen identification and integrity	§§ 493.1232;
	Specimen submission, handling, and referral	493.1242(a)(1) through (a)(6);
	Procedure manual	493.1251(b)(1)
§ 493.1103(b)	Specimen submission, handling, and referral	§§ 493.1242(a)(8) and (d);
	Procedure manual	493.1251(b)(1)
§ 493.1103(c)	Removed	
Test requisition:		
§ 493.1105—Introductory text	Retention requirements	§§ 493.1105(a)(1);
	Test request	493.1241(a), (b), (c), and (d)
§ 493.1105(a)	Test request	§ 493.1241(c)(2)
§ 493.1105(b)	Test request	§ 493.1241(c)(1)
§ 493.1105(c)	Test request	§ 493.1241(c)(4)
§ 493.1105(d)	Test request	§ 493.1241(c)(6)
§ 493.1105(e)	Test request	§ 493.1241(c)(3) and (c)(7)
§ 493.1105(f)	Test request	§§ 493.1241(c)(3), (c)(5), and (c)(8)
	Specimen submission, handling, and referral	493.1242(a)(3)
Test records:		
§ 493.1107—Introductory text	Retention requirements	§§ 493.1105(a)(3);
	Specimen identification and integrity	493.1232;
	Test records	493.1283(a)(4) and (b)
§ 493.1107(a)	Test records	§ 493.1283(a)(1)
§ 493.1107(b)	Specimen submission, handling, and referral	§§ 493.1242(b);
	Test records	493.1283(a)(2)
§ 493.1107(c)	Test records	§ 493.1283(a)(3)
§ 493.1107(d)	Test records	§ 493.1283(a)(4)
Test report:		
§ 493.1109—Introductory text	Retention requirements	§§ 493.1105(a)(3)(ii), (a)(6)(i), (a)(6)(ii) and (b);
	Postanalytic systems	493.1290;
	Test report	493.1291(b), (c)(3), and (f)
§ 493.1109(a)	Confidentiality of patient information	§§ 493.1231;
	Postanalytic systems	493.1290;
	Test report	493.1291(a) and (c)(3)
§ 493.1109(b)	Test report	§§ 493.1291(c)(2), (c)(4), and (c)(6)
§ 493.1109(c)	Test report	§ 493.1291(c)(7)
§ 493.1109(d)	Test report	§ 493.1291(d)
§ 493.1109(e)	Test report	§ 493.1291(f)
§ 493.1109(f)	Procedure manual	§§ 493.1251(b)(13);
	Test report	493.1291(g)

TABLE.—CROSSWALK—Continued

Former requirements and former sections (part 493, subparts J, K, M, and P)	Requirements in this final rule (part 493, subparts J, K, and M)	Sections in this final rule
§ 493.1109(g)	Test report	§ 493.1291(e)
§ 493.1109(h)	Test report	§ 493.1291(j)
Referral of specimens:		
§ 493.1111—Introductory text	Specimen submission, handling, and referral	§ 493.1242(c)
§ 493.1111(a)	Test report	§ 493.1291(i)(1)
§ 493.1111(b)	Test report	§ 493.1291(i)(2)
§ 493.1111(c)	Test report	§ 493.1291(i)(3)
General quality control; moderate complexity (including the subcategory) or high complexity testing, or any combination of these tests:		
§ 493.1201(a)	Removed	
§ 493.1201(a)(1)	Removed	
§ 493.1201(a)(2)	Facility Administration	§§ 493.1100
	General laboratory systems	493.1230
	Preanalytic systems	493.1240
	Analytic systems	493.1250
	Control Procedures	493.1256(d)
	Postanalytic systems	493.1290
§ 493.1201(b)	Analytic systems	§§ 493.1250;
	Procedure manual	493.1251(b)(7)
Moderate or high complexity testing, or both, Effective from September 1, 1992 to December 13, 2000:		
§ 493.1202(a)	Facility administration	§§ 493.1100;
	Subpart K—Quality systems for nonwaived testing.	493.1201 through 493.1227
§ 493.1202(b)	Facility administration	§§ 493.1100;
	Subpart K—Quality systems for nonwaived testing.	493.1201 through 493.1227
§ 493.1202(c)	Facility administration	§§ 493.1100;
	Subpart K—Quality systems for nonwaived testing.	493.1201 through 493.1227
§ 493.1202(c)(1)	Test systems, equipment, instruments, reagents, materials, and supplies.	§§ 493.1252(a);
	Maintenance and function checks	493.1254(a)(1) and (a)(2)
	Control procedures	493.1256(d)(2)
§ 493.1202(c)(2)	Procedure manual	§ 493.1251
§ 493.1202(c)(3)	Calibration and calibration verification procedures.	§ 493.1255
§ 493.1202(c)(4)	Control procedures	§ 493.1256
§ 493.1202(c)(5)	Control procedures	§ 493.1256(d)(1)
§ 493.1202(c)(6)	Corrective actions	§ 493.1282
§ 493.1202(c)(7)	Retention requirements	§ 493.1105(a)(3)
Moderate or high complexity testing, or both effective beginning 12/31/00:		
§ 493.1203—Introductory text	Removed	
§ 493.1203(a)	Removed	
§ 493.1203(b)	Removed	
Facilities:		
§ 493.1204—Introductory text	Facilities	§ 493.1101(a)
§ 493.1204(a)	Facilities	§§ 493.1101(a)(1) and (a)(2)
§ 493.1204(b)	Facilities	§ 493.1101(d)
Test methods, equipment, instrumentation, reagents, materials, and supplies:		
§ 493.1205—Introductory text	Facility Test systems, equipment, instruments, reagents, materials, and supplies.	§§ 493.1101(b); 493.1252
§ 493.1205(a)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(a)
§ 493.1205(b)	Facilities	§ 493.1101(b)
§ 493.1205(c)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(b)
§ 493.1205(c)(1)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(b)
§ 493.1205(c)(1)(i)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(b)(1)
§ 493.1205(c)(1)(ii)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(b)(2)
§ 493.1205(c)(1)(iii)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(b)(3)

TABLE.—CROSSWALK—Continued

Former requirements and former sections (part 493, subparts J, K, M, and P)	Requirements in this final rule (part 493, subparts J, K, and M)	Sections in this final rule
§ 493.1205(c)(1)(iv)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(b)(4)
§ 493.1205(c)(2)	Corrective actions	§ 493.1282(b)(3)
§ 493.1205(d)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(c)
§ 493.1205(d)(1)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(c)(1)
§ 493.1205(d)(2)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(c)(2)
§ 493.1205(d)(3)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(c)(3)
§ 493.1205(d)(4)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(c)(4)
§ 493.1205(e)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(d)
§ 493.1205(e)(1)	Test systems, equipment, instruments, reagents, materials, and supplies.	§§ 493.1252(d);
	Immunohematology	493.1271(b)
§ 493.1205(e)(2)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(e)
Procedure manual:		
§ 493.1211(a)	Procedure manual	§ 493.1251(a)
§ 493.1211(b)	Procedure manual	§ 493.1251(b)
§ 493.1211(b)(1)	Procedure manual	§ 493.1251(b)(1)
§ 493.1211(b)(2)	Procedure manual	§ 493.1251(b)(2)
§ 493.1211(b)(3)	Procedure manual	§§ 493.1251(b)(3);
	Histocompatibility	493.1278(d)(7)
§ 493.1211(b)(4)	Procedure manual	§ 493.1251(b)(4)
§ 493.1211(b)(5)	Procedure manual	§ 493.1251(b)(5)
§ 493.1211(b)(6)	Procedure manual	§ 493.1251(b)(6)
§ 493.1211(b)(7)	Procedure manual	§ 493.1251(b)(7)
§ 493.1211(b)(8)	Procedure manual	§ 493.1251(b)(8)
§ 493.1211(b)(9)	Procedure manual	§ 493.1251(b)(9)
§ 493.1211(b)(10)	Procedure manual	§ 493.1251(b)(10)
§ 493.1211(b)(11)	Procedure manual	§ 493.1251(b)(11)
§ 493.1211(b)(12)	Procedure manual	§ 493.1251(b)(12)
§ 493.1211(b)(13)	Specimen submission, handling, and referral	§§ 493.1242(a)(4);
	Procedure manual	493.1251(b)(1)
§ 493.1211(b)(14)	Procedure manual	§ 493.1251(b)(13)
§ 493.1211(b)(15)	Procedure manual	§ 493.1251(b)(14)
§ 493.1211(b)(16)	Procedure manual	§ 493.1251(b)(1)
§ 493.1211(c)	Procedure manual	§ 493.1251(c)
§ 493.1211(d)	Procedure manual	§ 493.1251(d)
§ 493.1211(e)	Procedure manual	§ 493.1251(d)
§ 493.1211(f)	Procedure manual	§ 493.1251(d)
§ 493.1211(g)	Retention requirements	§§ 493.1105(a)(2);
	Procedure manual	493.1251(e)
Establishment and verification of method performance specifications:		
§ 493.1213—Introductory text	Removed	
§ 493.1213(a)	Establishment and verification of performance specifications.	§ 493.1253(a)
§ 493.1213(b)(1)	Removed	
§ 493.1213(b)(2)	Establishment and verification of performance specifications.	§§ 493.1253(b)(1) and (2)
§ 493.1213(b)(2)(i)	Establishment and verification of performance specifications.	§§ 493.1253(b)(1) and (b)(2)
§ 493.1213(b)(2)(i)(A)	Establishment and verification of performance specifications.	§§ 493.1253(b)(1)(i)(A) and (b)(2)(i)
§ 493.1213(b)(2)(i)(B)	Establishment and verification of performance specifications.	§§ 493.1253(b)(1)(i)(B) and (b)(2)(ii)
§ 493.1213(b)(2)(i)(C)	Establishment and verification of performance specifications.	§ 493.1253(b)(2)(iii)
§ 493.1213(b)(2)(i)(D)	Establishment and verification of performance specifications.	§ 493.1253(b)(2)(iv)
§ 493.1213(b)(2)(i)(E)	Establishment and verification of performance specifications.	§§ 493.1253(b)(1)(i)(C) and (b)(2)(v)
§ 493.1213(b)(2)(i)(F)	Establishment and verification of performance specifications.	§§ 493.1253(b)(1)(ii) and (b)(2)(vi)
§ 493.1213(b)(2)(i)(G)	Establishment and verification of performance specifications.	§ 493.1253(b)(2)(vii)

TABLE.—CROSSWALK—Continued

Former requirements and former sections (part 493, subparts J, K, M, and P)	Requirements in this final rule (part 493, subparts J, K, and M)	Sections in this final rule
§ 493.1213(b)(2)(ii)	Establishment and verification of performance specifications.	§ 493.1253(b)(3)
§ 493.1213(c)	Establishment and verification of performance specifications.	§ 493.1253(c)
Equipment maintenance and function checks:		
§ 493.1215—Introductory text	Removed	
§ 493.1215(a)—Title only	Removed	
§ 493.1215(a)(1)	Removed	
§ 493.1215(a)(1)(i)	Removed	
§ 493.1215(a)(1)(ii)	Removed	
§ 493.1215(a)(2)—Lead-in only	Removed	
§ 493.1215(a)(2)(i)	Maintenance and function checks	§ 493.1254(b)(1)(i)
§ 493.1215(a)(2)(ii)	Maintenance and function checks	§ 493.1254(b)(1)(ii)
§ 493.1215(a)(2)(iii)	Maintenance and function checks	§ 493.1254(b)(1)(ii)
§ 493.1215(b)	Removed	
§ 493.1215(b)(1)	Removed	
§ 493.1215(b)(1)(i)	Removed	
§ 493.1215(b)(1)(ii)	Removed	
§ 493.1215(b)(2)	Removed	
§ 493.1215(b)(2)(i)	Maintenance and function checks	§ 493.1254(b)(2)(i)
§ 493.1215(b)(2)(ii)	Maintenance and function checks	§ 493.1254(b)(2)(ii)
§ 493.1215(b)(2)(iii)	Maintenance and function checks	§ 493.1254(b)(2)(ii)
Calibration and calibration verification procedures:		
§ 493.1217—Introductory text	General Provisions—Definitions Calibration and calibration verification procedures.	§§ 493.2; 493.1255
§ 493.1217(a)	Removed	
§ 493.1217(b)—Lead-in only	Removed	
§ 493.1217(b)(1)	Calibration and calibration verification procedures.	§ 493.1255(a)
§ 493.1217(b)(1)(i)	Calibration and calibration verification procedures.	§ 493.1255(a)(1)
§ 493.1217(b)(1)(ii)	Calibration and calibration verification procedures.	§ 493.1255(a)(2)
§ 493.1217(b)(1)(ii)(A)	Calibration and calibration verification procedures.	§ 493.1255(a)(2)(ii)
§ 493.1217(b)(1)(ii)(B)	Calibration and calibration verification procedures.	§ 493.1255(a)(2)(i)
§ 493.1217(b)(1)(iii)	Calibration and calibration verification procedures.	§ 493.1255(a)(3)
§ 493.1217(b)(2)	Calibration and calibration verification procedures.	§ 493.1255(b)
§ 493.1217(b)(2)(i)	Calibration and calibration verification procedures.	§ 493.1255(b)(1)
§ 493.1217(b)(2)(ii)	Calibration and calibration verification procedures.	§ 493.1255(b)(2)
§ 493.1217(b)(2)(ii)(A)	Calibration and calibration verification procedures.	§ 493.1255(b)(2)(i)
§ 493.1217(b)(2)(ii)(B)	Removed	
§ 493.1217(b)(2)(ii)(B)(1)	Removed	
§ 493.1217(b)(2)(ii)(B)(2)	Calibration and calibration verification procedures.	§ 493.1255(b)(2)(ii)
§ 493.1217(b)(2)(ii)(C)	Calibration and calibration verification procedures.	§ 493.1255(b)(3)
§ 493.1217(b)(2)(ii)(C)(1)	Calibration and calibration verification procedures.	§ 493.1255(b)(3)(i)
§ 493.1217(b)(2)(ii)(C)(2)	Calibration and calibration verification procedures.	§ 493.1255(b)(3)(ii)
§ 493.1217(b)(2)(ii)(C)(3)	Calibration and calibration verification procedures.	§ 493.1255(b)(3)(iii)
§ 493.1217(b)(2)(ii)(C)(4)	Calibration and calibration verification procedures.	§ 493.1255(b)(3)(iv)
§ 493.1217(b)(3)	Calibration and calibration verification procedures.	§ 493.1255(a) and (b)
Control procedures:		
§ 493.1218	Control procedures	§ 493.1256(a)
§ 493.1218(a)	Removed	
§ 493.1218(b)—Partial removed	Control procedures	§ 493.1256(b), (c)(1), and (c)(2)
§ 493.1218(b)(1)	Control procedures	§ 493.1256(d)(3)(ii)
§ 493.1218(b)(2)	Control procedures	§ 493.1256(d)(3)(i)
§ 493.1218(b)(3)	Control procedures	§ 493.1256(d)(5)

TABLE.—CROSSWALK—Continued

Former requirements and former sections (part 493, subparts J, K, M, and P)	Requirements in this final rule (part 493, subparts J, K, and M)	Sections in this final rule
§ 493.1218(b)(3)(i)	Control procedures	§ 493.1256(d)(5)
§ 493.1218(b)(3)(ii)	Control procedures	§ 493.1256(d)(5)
§ 493.1218(b)(4)	Control procedures	§§ 493.1256(d)(3)(ii) and (d)(3)(iv)
§ 493.1218(b)(5)	Control procedures	§ 493.1256(h)
§ 493.1218(c)	Control procedures	§ 493.1256(d)(8)
§ 493.1218(d)	Control procedures	§ 493.1256(d)(10)(i)
§ 493.1218(d)(1)	Control procedures	§ 493.1256(d)(10)(ii)
§ 493.1218(d)(2)	Control procedures	§ 493.1256(d)(10)(iii)
§ 493.1218(e)	Control procedures	§ 493.1256(f)
§ 493.1218(f)	Control procedures	§ 493.1256(e)
§ 493.1218(f)(1)	Control procedures	§ 493.1256(e)(1)
§ 493.1218(f)(2)	Control procedures	§ 493.1256(e)(2)
§ 493.1218(f)(3)	Control procedures	§§ 493.1256(e)(3);
	Histopathology	493.1273(a)
§ 493.1218(f)(4)	Control procedures	§ 493.1256(e)(4)(5)
Remedial actions:		
§ 493.1219—Introductory text	Corrective actions	§ 493.1282(a) and (b)
§ 493.1219(a)	Corrective actions	§ 493.1282(b)(1)
§ 493.1219(a)(1)	Corrective actions	§ 493.1282(b)(1)(i)
§ 493.1219(a)(2)	Corrective actions	§ 493.1282(b)(1)(ii)
§ 493.1219(a)(3)	Corrective actions	§ 493.1282(b)(1)(iii)
§ 493.1219(b)	Corrective actions	§ 493.1282(b)(2)
§ 493.1219(c)	Test report	§ 493.1291(h)
§ 493.1219(d)	Test report	§ 493.1291(k)
§ 493.1219(d)(1)	Test report	§ 493.1291(k)(1)
§ 493.1219(d)(2)	Test report	§ 493.1291(k)(2)
§ 493.1219(d)(3)	Retention requirements	§§ 493.1105(a)(6);
	Test report	493.1291(k)(3)
Quality control records:		
§ 493.1221	Retention requirements	§ 493.1101(e); 493.1105(a)(3)(i) through (a)(3)(ii);
	Test systems, equipment, instruments, reagents, material, and supplies performance.	493.1252(b);
	Establishment and verification of performance	493.1253(c);
	Maintenance and function checks	493.1254(a), (b)(1)(ii), and (b)(2)(ii);
	Calibration and calibration verification procedures.	493.1255(a) and (b);
	Control procedures	493.1256(g);
	Bacteriology	493.1261(c);
	Mycobacteriology	493.1262(c);
	Mycology	493.1263(c);
	Parasitology	493.1264(d);
	Virology	493.1265(b);
	Routine chemistry	493.1267(d);
	Hematology	493.1269(d);
	Immunohematology	493.1271(f);
	Histopathology	493.1273(f);
	Cytology	493.1274(h);
	Clinical Cytogenetics	493.1276(e);
	Histocompatibility	493.1278(g)
Quality control-specialties and subspecialties for tests of moderate or high complexity; or both:		
§ 493.1223	Control Procedures	§§ 493.1256(a), (b), (c), (d)(1), and (2);
Microbiology:		
§ 493.1225	Removed	
Bacteriology:		
§ 493.1227—Introductory text	Bacteriology	§ 493.1201
§ 493.1227(a)—Partially removed	Bacteriology	§ 493.1261(a)
Bacteriology:		
§ 493.1227(a)(1)—Partially removed	Control procedures	§§ 493.1256(d)(3)(ii), (d)(3)(iv), and (e)(1);
	Bacteriology	493.1261(a)(1)
§ 493.1227(a)(2)	Control procedures	§§ 493.1256(e)(1) and (e)(2);
	Bacteriology	493.1261(a)(2)
§ 493.1227(a)(3)	Bacteriology	§ 493.1261(a)(3)
§ 493.1227(b)	Control procedures	§ 493.1256(e)(1)
§ 493.1227(c)	Bacteriology	§ 493.1261(b)
§ 493.1227(c)(1)	Bacteriology	§ 493.1261(b)(2)
§ 493.1227(c)(2)	Bacteriology	§ 493.1261(b)(1)
Mycobacteriology:		
§ 493.1229—Introductory text	Mycobacteriology	§ 493.1202

TABLE.—CROSSWALK—Continued

Former requirements and former sections (part 493, subparts J, K, M, and P)	Requirements in this final rule (part 493, subparts J, K, and M)	Sections in this final rule
§ 493.1229(a)	Mycobacteriology	§ 493.1262(a)
§ 493.1229(b)	Control procedures	§ 493.1256(e)(3)
§ 493.1229(c)	Control procedures	§§ 493.1256(e)(2);
	Mycobacteriology	493.1262(a)
§ 493.1229(d)	Mycobacteriology	§§ 493.1262(b)(1) through (b)(3)
Mycology:		
§ 493.1231—Introductory text	Mycology	§ 493.1203
§ 493.1231(a)	Control procedures	§§ 493.1256(e)(1) and (e)(4)
§§ 493.1231(b)	Control procedures	§ 493.1256(e)(1)
§ 493.1231(c)	Control procedures	§ 493.1256(e)(2)
§ 493.1231(d)	Mycology	§§ 493.1263(b)(1) through (b)(3)
Parasitology:		
§ 493.1233—Introductory text	Parasitology	§ 493.1204
§ 493.1233(a)	Parasitology	§ 493.1264(a)
§ 493.1233(b)	Parasitology	§ 493.1264(b)
§ 493.1233(c)	Parasitology	§ 493.1264(c)
Virology:		
§ 493.1235—Introductory text	Virology	§ 493.1205
§ 493.1235(a)	Facilities	§§ 493.1101(b);
	Test systems, equipment, instruments, reagents, material, and supplies.	493.1252(a)
§ 493.1235(b)	Virology	§§ 493.1265(b);
	Test records	493.1283(a)(4)
§ 493.1235(c)	Virology	§ 493.1265(a)
Diagnostic immunology:		
§ 493.1237	Removed	
Syphilis serology:		
§ 493.1239—Introductory text	Syphilis serology	§ 493.1207
§ 493.1239(a)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(a)
§ 493.1239(b)	Control procedures	§ 493.1256(d)(3)(iii)
§ 493.1239(c)	Control procedures	§§ 493.1256(a) and (d)(3)(ii);
§ 493.1239(d)	Control procedures	§ 493.1256(f)
§ 493.1239(e)	Immunohematology	§ 493.1271(b)
General immunology:		
§ 493.1241	General immunology	§ 493.1208
§ 493.1241(a)	Control procedures	§ 493.1256(d)(3)(iii)
§ 493.1241(b)	Control procedures	§ 493.1256(a)
§ 493.1241(c)	Control procedures	§ 493.1256(f)
§ 493.1241(d)—Lead-in only	Removed	
§ 493.1241(d)(1)	Immunohematology	§ 493.1271(b)
§ 493.1241(d)(2)	Immunohematology	§ 493.1271(b)
Chemistry:		
§ 493.1243	Removed	
Routine chemistry:		
§ 493.1245—Introductory text	Routine chemistry	§§ 493.1210; 493.1267
§ 493.1245(a)	Routine chemistry	§ 493.1267(a)
§ 493.1245(b)	Routine chemistry	§ 493.1267(b)
§ 493.1245(c)	Routine chemistry	§ 493.1267(b)
§ 493.1245(d)	Routine chemistry	§ 493.1267(c)
Endocrinology:		
§ 493.1247	Endocrinology	§ 493.1212
Toxicology:		
§ 493.1249—Introductory text	Toxicology	§§ 493.1213;
	Control procedures	493.1256(d)(4)
§ 493.1249(a)	Control procedures	§ 493.1256(d)(4)(i)
§ 493.1249(b)	Control procedures	§ 493.1256(d)(4)(ii)
Urinalysis:		
§ 493.1251—Introductory text only	Urinalysis	§ 493.1211
Hematology:		
§ 493.1253	Hematology	§ 493.1215
§ 493.1253(a)	Hematology	§§ 493.1269(a)(1) and (a)(2)
§ 493.1253(b)	Control procedures	§ 493.1256(d)
§ 493.1253(c)	Hematology	§ 493.1269(b)
§ 493.1253(d)	Hematology	§ 493.1269(c)
§ 493.1253(d)(1)	Hematology	§ 493.1269(c)(1)
§ 493.1253(d)(2)	Hematology	§ 493.1269(c)(2)
Pathology:		
§ 493.1255	Removed	
Cytology:		
§ 493.1257—Introductory text	Cytology	§ 493.1221

TABLE.—CROSSWALK—Continued

Former requirements and former sections (part 493, subparts J, K, M, and P)	Requirements in this final rule (part 493, subparts J, K, and M)	Sections in this final rule
§ 493.1257(a)	Cytology	§ 493.1274(b)
§ 493.1257(a)(1)	Cytology	§ 493.1274(b)(1)
§ 493.1257(a)(2)	Cytology	§ 493.1274(b)(2)
§ 493.1257(a)(3)	Cytology	§ 493.1274(b)(3)
§ 493.1257(a)(4)	Cytology	§ 493.1274(e)(4)
§ 493.1257(a)(5)	Cytology	§ 493.1274(a)
§ 493.1257(b)	Cytology	§ 493.1274(d)
§ 493.1257(b)(1)	Cytology	§§ 493.1274(d)(2) and (d)(2)(iv)
§ 493.1257(b)(2)	Cytology	§ 493.1274(d)(2)(iii)
§ 493.1257(b)(3)	Cytology	§ 493.1274(g)
§ 493.1257(b)(3)(i)	Cytology	§ 493.1274(d)(2)(i)
§ 493.1257(b)(3)(ii)	Cytology	§ 493.1274(d)(2)(ii)
§ 493.1257(c)	Cytology	§ 493.1274(e)(1)
§ 493.1257(c)(1)	Cytology	§§ 493.1274(e)(1)(i) through (e)(1)(v), and (e)(2)
§ 493.1257(c)(2)	Cytology	§ 493.1274(e)(3)
§ 493.1257(c)(3)	Cytology	§ 493.1274(d)(1)(i)(B)
§ 493.1257(c)(4)	Cytology	§ 493.1274(d)(1)
§ 493.1257(c)(4)(i)	Cytology	§§ 493.1274(d)(1)(i) and (d)(4)
§ 493.1257(c)(4)(ii)	Cytology	§ 493.1274(d)(1)(ii)
§ 493.1257(d)	Cytology	§ 493.1274(c)
§ 493.1257(d)(1)	Cytology	§ 493.1274(c)(1)
§ 493.1257(d)(1)(i)	Cytology	§ 493.1274(c)(1)(i)
§ 493.1257(d)(1)(ii)	Cytology	§ 493.1274(c)(4)
§ 493.1257(d)(1)(iii)	Cytology	§ 493.1274(c)(1)(ii)
§ 493.1257(d)(2)	Cytology	§ 493.1274(c)(2)
§ 493.1257(d)(3)	Cytology	§ 493.1274(c)(3)
§ 493.1257(d)(4)	Cytology	§§ 493.1274(c)(5)(i) through (c)(5)(vi)
§ 493.1257(d)(5)	Cytology	§ 493.1274(c)(6)
§ 493.1257(e)—Lead-in only	Removed	
§ 493.1257(e)(1)	Cytology	§ 493.1274(e)(4)
§ 493.1257(e)(2)	Cytology	§ 493.1274(e)(5)
§ 493.1257(f)	Cytology	§ 493.1274(e)(6)
§ 493.1257(g)	Retention requirements, Cytology	§§ 493.1105(a)(7)(i)(A); 493.1274(f)(2) through (f)(4)
Histopathology:		
§ 493.1259—Introductory text	Histopathology	§ 493.1219
§ 493.1259(a)	Histopathology	§ 493.1273(a)
§ 493.1259(b)	Retention requirements, Histopathology	§§ 493.1105(a)(7)(i)(B) and (a)(7)(ii); 493.1273(b)
§ 493.1259(c)	Facilities; Retention requirements, Histopathology.	§§ 493.1101(e); 493.1105(a)(7)(iii); 493.1273(b)
§ 493.1259(d)	Histopathology	§ 493.1273(d)
§ 493.1259(e)	Histopathology	§ 493.1273(e)
Oral pathology:		
§ 493.1261	Oral pathology	§ 493.1220
Radiobioassay:		
§ 493.1263	Radiobioassay	§ 493.1226
Histocompatibility:		
§ 493.1265—Introductory text	Histocompatibility	§ 493.1227
§ 493.1265(a)	Histocompatibility	§ 493.1278(f)
§ 493.1265(a)(1)	Histocompatibility	§ 493.1278(e)(2)
§ 493.1265(a)(1)(i)	Histocompatibility	§ 493.1278(e)(2)(i)
§ 493.1265(a)(1)(ii)	Histocompatibility; Procedure manual	§§ 493.1278(e)(1); 493.1251(b)(3)
§ 493.1265(a)(1)(iii)	Histocompatibility	§ 493.1278(e)(2)(ii)
§ 493.1265(a)(1)(iv)	Procedure manual	§§ 493.1251(b)(3) and (b)(13)
§ 493.1265(a)(2)	Histocompatibility	§ 493.1278(f)
§ 493.1265(a)(2)(i)	Histocompatibility	§ 493.1278(f)(2)
§ 493.1265(a)(2)(ii)	Histocompatibility	§§ 493.1278(d)(4) through (d)(5)
§ 493.1265(a)(3)—Lead-in only	Removed	
§ 493.1265(a)(3)(i)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(b);
	Specimen submission, handling, and referral	§ 493.1242(a)(4)
§ 493.1265(a)(3)(ii)	Histocompatibility	§ 493.1278(a)(1)
§ 493.1265(a)(3)(iii)—Partially removed	Specimen identification and integrity, Histocompatibility; Test records.	§§ 493.1232; 493.1278(a)(2) 493.1283(a)(1)
§ 493.1265(a)(4)	Histocompatibility	§ 493.1278(a)(3)
§ 493.1265(a)(5)	Test systems, equipment, instruments, reagents, materials, and supplies.	§§ 493.1252(c)(1) through (c)(4)
§ 493.1265(a)(6)	Histocompatibility	§ 493.1278(b)
§ 493.1265(a)(6)(i)	Histocompatibility	§ 493.1278(b)(2)

TABLE.—CROSSWALK—Continued

Former requirements and former sections (part 493, subparts J, K, M, and P)	Requirements in this final rule (part 493, subparts J, K, and M)	Sections in this final rule
§ 493.1265(a)(6)(ii)	Histocompatibility	§ 493.1278(b)(3)
§ 493.1265(a)(6)(iii)	Histocompatibility	§ 493.1278(b)(5)(v)
§ 493.1265(a)(7)	Histocompatibility	§ 493.1278(b)(5)
§ 493.1265(a)(7)(i)	Histocompatibility	§ 493.1278(b)(5)(i)
§ 493.1265(a)(7)(ii)	Histocompatibility	§ 493.1278(b)(5)(ii)
§ 493.1265(a)(7)(iii)	Histocompatibility	§ 493.1278(b)(5)(iv)
§ 493.1265(a)(7)(iv)	Histocompatibility	§ 493.1278(b)(5)(iii)
§ 493.1265(a)(8)	Histocompatibility	§ 493.1278(d)
§ 493.1265(a)(8)(i)	Histocompatibility	§ 493.1278(d)(5)
§ 493.1265(a)(8)(i)(A)	Histocompatibility	§ 493.1278(d)(5)
§ 493.1265(a)(8)(i)(B)	Histocompatibility	§ 493.1278(d)(5)
§ 493.1265(a)(8)(ii)	Histocompatibility	§ 493.1278(d)(3)
§ 493.1265(a)(8)(ii)(A)	Histocompatibility	§ 493.1278(d)(3)
§ 493.1265(a)(8)(ii)(B)	Test systems, equipment, instruments, reagents, materials, and supplies.	§ 493.1252(b)
§ 493.1265(a)(9)—Lead-in only	Removed	
§ 493.1265(a)(9)(i)	Histocompatibility	§§ 493.1278(b)(6) and (d)(6)
§ 493.1265(a)(9)(i)(A)	Histocompatibility	§§ 493.1278(b)(6)(i) and (d)(6)(i)
§ 493.1265(a)(9)(i)(B)	Histocompatibility	§§ 493.1278(b)(6)(ii) and (d)(6)(ii)
§ 493.1265(a)(9)(i)(C)	Histocompatibility	§ 493.1278(b)(6)(iii)
§ 493.1265(a)(9)(ii)	Histocompatibility	§§ 493.1278(c) and (e)(3)
§ 493.1265(a)(10)	Histocompatibility	§§ 493.1278(a) and (f)
§ 493.1265(a)(11)	Immunohematology	§ 493.1271
§ 493.1265(a)(12)	Histocompatibility	§ 493.1278(a)(4)
§ 493.1265(a)(13)	Removed	
§ 493.1265(a)(14)	Histocompatibility	§ 493.1278(a)(5)
§ 493.1265(b)	Histocompatibility	§ 493.1278(f)
§ 493.1265(b)(1)	Histocompatibility	§ 493.1278(f)(1)
§ 493.1265(b)(2)	Histocompatibility	§ 493.1278(f)(1)
§ 493.1265(b)(3)	Histocompatibility	§ 493.1278(f)(3)
§ 493.1265(c)	Histocompatibility	§§ 493.1278(a) through (c)
§ 493.1265(d)	Immunohematology	§ 493.1271(b)
Clinical cytogenetics:		
§ 493.1267—Introductory text	Clinical cytogenetics	§ 493.1225
§ 493.1267(a)	Cytogenetics	§ 493.1276(c)
§ 493.1267(b)	Cytogenetics	§§ 493.1276(b)(1) through (b)(3)
§ 493.1267(c)	Cytogenetics	§ 493.1276(a)
§ 493.1267(d)	Cytogenetics	§ 493.1276(d)
Immunohematology:		
§ 493.1269—Introductory text	Immunohematology	§ 493.1217
§ 493.1269(a)	Immunohematology	§ 493.1271(a)(1)
§ 493.1269(b)	Immunohematology	§ 493.1271(a)(2)
§ 493.1269(c)	Immunohematology	§ 493.1271(a)(3)
§ 493.1269(d)	Immunohematology	§ 493.1271(a)
Transfusion services and bloodbanking:		
§ 493.1271—Partially removed	Requirements for transfusion services and Subpart M.	§ 493.1103; § 493.1449(b) and (q)
Immunohematological collection, processing, dating periods, labeling and distribution of blood and blood products:		
§ 493.1273—Introductory text	Immunohematology	§ 493.1271(b)
§ 493.1273(a)	Immunohematology	§ 493.1271(b)
§ 493.1273(b)	Immunohematology	§ 493.1271(b)
§ 493.1273(c)	Immunohematology	§ 493.1271(b)
§ 493.1273(d)	Requirements for transfusion services	§ 493.1103(c)(2)
Blood and blood products storage facilities:		
§ 493.1275(a)	Immunohematology	§ 493.1271(c)
§ 493.1275(a)(1)	Immunohematology	§ 493.1271(c)(1)
§ 493.1275(a)(2)	Immunohematology	§ 493.1271(c)(2)
§ 493.1275(b)	Requirements for transfusion services	§ 493.1103(c)(1)
Arrangement for services:		
§ 493.1277	Requirements for transfusion services	§ 493.1103(a)
Provision of testing:		
§ 493.1279—Partially removed	Requirements for transfusion services	§§ 493.1103(b)
Retention of samples of transfused blood:		
§ 493.1283	Immunohematology	§ 493.1271(d)
Investigation of transfusion reactions:		
§ 493.1285	Requirements for transfusion services; Immunohematology.	§§ 493.1103(d); 493.1271(e)(1)and (e)(2)

TABLE.—CROSSWALK—Continued

Former requirements and former sections (part 493, subparts J, K, M, and P)	Requirements in this final rule (part 493, subparts J, K, and M)	Sections in this final rule
Quality assurance for Moderate Complexity (including the Subcategory) or High Complexity Testing, or Any Combination of These Tests:		
§ 493.1701	Introduction; General laboratory systems; General laboratory systems assessment; Preanalytic Systems; Test request; Preanalytic systems assessment; Analytic Systems; Analytic systems assessment; Postanalytic Systems; Postanalytic systems assessment.	§§ 493.1200; 493.1230; 493.1239; 493.1240; 493.1241(e); 493.1249; 493.1250; 493.1289; 493.1290; 493.1299
Patient test management assessment:		
§ 493.1703—Introductory text	General laboratory systems; General laboratory systems assessment; Preanalytic Systems; Preanalytic systems assessment; Postanalytic Systems; Postanalytic systems assessment.	§§ 493.1230; 493.1239(a) and (b); 493.1240; 493.1249(a) and (b); 493.1290; 493.1299(a) and (b)
§ 493.1703(a)	Preanalytic systems assessment	§§ 493.1249(a) and (b)
§ 493.1703(b)	Preanalytic systems assessment	§§ 493.1249(a) and (b)
§ 493.1703(c)	Preanalytic systems assessment	§§ 493.1249(a) and (b)
§ 493.1703(d)	Postanalytic systems assessment	§§ 493.1299(a) and (b)
§ 493.1703(e)	Test Report; Postanalytic systems assessment.	§§ 493.1291(a), (g), and (h); 493.1299(a) and (b)
§ 493.1703(f)	Facilities; Postanalytic systems assessment	§§ 493.1101(e) 493.1299(a) and (b)
Quality control assessment:		
§ 493.1705—Introductory text	Analytic Systems; Analytic system assessment.	§§ 493.1250; 493.1289(a) and (b)
§ 493.1705(a)	Analytic system assessment	§§ 493.1289(a) and (b)
§ 493.1705(b)	Analytic system assessment	§§ 493.1289(a) and (b)
§ 493.1705(c)	Analytic system assessment; Postanalytic systems assessment.	§§ 493.1289(a) and (b); 493.1299(a) and (b)
Proficiency testing assessment:		
§ 493.1707	General laboratory systems; Evaluation of proficiency testing; General laboratory systems assessment.	§§ 493.1230; 493.1236(a)(1); 493.1239(a) and (b)
Comparison of test results:		
§ 493.1709		
§ 493.1709(a)	Comparison of test results	§ 493.1281(a)
§ 493.1709(b)	Evaluation of proficiency testing	§ 493.1236(c)(1)
Relationship of patient information to patient test results:		
§ 493.1711—Introductory text	Comparison of test results; Analytic systems assessment.	§§ 493.1281(b); 493.1289(a) and (b)
§ 493.1711(a)	Comparison of test results	§ 493.1281(b)(1)
§ 493.1711(b)	Comparison of test results	§ 493.1281(b)(2)
§ 493.1711(c)	Comparison of test results	§ 493.1281(b)(3)
§ 493.1711(d)	Comparison of test results	§ 493.1281(b)(4)
§ 493.1711(e)	Comparison of test results; Analytic systems assessment.	§§ 493.1281(b)(5); 493.1289(a) and (b)
Personnel assessment:		
§ 493.1713	Personnel competency assessment policies; General laboratory systems assessment.	§§ 493.1235; 493.1239(a) and (b)
Communications:		
§ 493.1715	Communications; General laboratory systems assessment.	§§ 493.1234; 493.1239(a) and (b)
Complaint investigations:		
§ 493.1717	Complaint investigations; General laboratory systems assessment.	§§ 493.1233; 493.1239(a) and (b)
Quality assurance review with staff:		
§ 493.1719	General laboratory systems assessment; Preanalytic systems assessment; Analytic systems assessment; Postanalytic systems assessment.	§§ 493.1239(b) and (c); 493.1249(b) and (c); 493.1289(b) and (c); 493.1299(b) and (c)
Quality assurance records:		
§ 493.1721	Retention requirements; General laboratory systems assessment; Analytic systems assessment.	§§ 493.1105(a)(5) and (b); 493.1239(c); 493.1249(c); 493.1289(c); 493.1299(c)

IV. Analysis and Responses to Public Comments

We received numerous comments on the final rule with comment period published on February 28, 1992 in the **Federal Register**. These comments were from State agencies, proficiency testing programs, professional organizations, the Clinical Laboratory Improvement Advisory Committee (CLIAC), laboratories, physicians, and the general public. Summaries of the public comments received and our responses to those comments are set forth below.

Subpart I—Proficiency Testing Programs for Tests of Moderate Complexity (Including the Subcategory), High Complexity, or Any Combination of These Tests

We received a number of comments on the topic of proficiency testing. We intend to publish a notice of proposed rulemaking addressing proficiency testing issues in more detail in the future. We have, however, determined that it would be appropriate to include in this final rule a change that we believe is necessary to improve the operation of the CLIA proficiency testing program, related to the percentage of required agreement among participant or reference laboratories. Thus, we are addressing only one of the changes requested by the commenters and recommended by the CLIAC.

Specific comments received and response to comments regarding subpart I are set forth below.

Comment: A few commenters, professional organizations, and proficiency testing programs expressed their concerns over the change to a 90 percent consensus requirement to be reached before a proficiency testing sample could be graded. Commenters felt there should be a grade assigned to their samples. One commenter stated that their laboratory paid for samples, so grading should be required. Proficiency testing programs had similar opinions. The CLIAC recommended reducing the consensus required for grading proficiency testing challenges to decrease the number of ungradeable samples as ungraded proficiency testing is not effective in assisting laboratories in their quality assessment of test performance.

Response: We agree with the commenters and are changing the percentage of required agreement among participant or referee laboratories to 80 percent in the specialties and subspecialties where 90 percent agreement was previously required.

Subpart J—Patient Test Management for Moderate Complexity (Including the Subcategory), High Complexity, or Any Combination of These Tests

Following publication of the final rule with comment period, we received approximately 150 comments regarding subpart J. The comments were in response to the requirements for specimen submission and handling; test requisition including oral requests and authorized persons; and test records and test reports, including confidentiality and referral of specimens. The majority of the commenters disagreed with some portion of the requirements and some commenters requested clarification of certain requirements while others offered specific revised language.

Specific comments received and responses to comments regarding subpart J are set forth below.

Comment: A number of State agencies disagreed with our removal of the requirement that laboratories comply with applicable Federal, State, and local laws.

Response: We agree with the commenters and are reinstating the requirement now at § 493.1101(c). As part of the partnering relationship with State agencies and local governments, the reinstatement of this requirement will allow us to support a State or local government that seeks to protect the public from actions it finds would be detrimental to public health.

Comment: Some commenters disagreed with requiring written authorization for oral test requests, describing the difficulties that this requirement causes.

Response: We acknowledge that when a laboratory asks that an oral request for patient testing be followed with a written request, there is no guarantee that one will be received. On January 19, 1993, we published a technical correction in the **Federal Register** (58 FR 5215) and (58 FR 5229) that amended the requirement formerly at § 493.1105. This requirement, now at § 493.1241(b), states that oral requests for laboratory tests are permitted only if the laboratory requests written or electronic authorization for testing within 30 days of the oral request and documents the efforts made to obtain a written or electronic authorization.

Comment: We received several comments recommending information the laboratory should solicit and obtain on the test requisition. Specifically, the commenters believe the age and sex of the patient, time of specimen collection, and the specimen source should be included since they are pertinent to either how the laboratory processes the specimen and/or how the test results are interpreted.

Response: We agree with the commenters. The requirement, formerly at § 493.1105(f), requires the laboratory to ensure that the requisition or test authorization includes any additional information relevant and necessary for accurate and timely testing and result reporting (for clarity, we are adding ''interpretation'' if applicable to this requirement). The requirement, now at § 493.1241(c)(3), specifies that the laboratory must request the patient's sex and age or date of birth as normal values and interpretation of test results are often dependent on this information. Concurrently, we are redesignating age or date of birth requirements, formerly at § 493.1105(e), for Pap smear requisitions to test requests (now at § 493.1241(c)(3)). The time of specimen collection must also be requested when it is relevant for the testing to be performed. For example, this information is important when interpreting the results of peak and trough therapeutic drug assays. In addition, we are requiring that specimen source, when appropriate, be solicited on the test requisition. Specimen handling, preservation, and preparation (for example, use of proper transfer media, inoculation of media in microbiology and clinical cytogenetics, and the application of appropriate normal values reported with patient test results) are dependent on the origin of the specimen. Therefore, we are including specimen source, when appropriate, as part of the laboratory's submission, handling, and referral procedures (now at § 493.1242(a)(3)). We are also requiring specimen source to be included on the test report if warranted (now at § 493.1291(c)(5)). This routine laboratory practice was inadvertently omitted from the final rule with comment period.

Comment: One organization representing members of the laboratory community objected to the amount of information that a laboratory must have on the test requisition, specifically the information that is needed when submitting a Pap smear. The organization stated that laboratories do not have access to patient records and are dependent on the authorized person ordering the test to provide this information. The organization agreed the information was important but assumed we would prohibit testing if all information was not obtained by the laboratory.

Response: We agree with the commenter that the information being requested is important. Therefore, we are retaining the test request

requirements formerly at § 493.1105, (now at § 493.1241(c)) as relevant information necessary for proper test performance and interpretation. The test requisition requirements do not prohibit laboratories from performing the testing if the requested information is missing. Although we expect laboratories to obtain this information when possible, the potential negative impact of the missing information on the test results may be addressed or noted on the report.

Comment: One State health department requested modification of the requirement for recording the time of specimen receipt into the laboratory, stating we should require the time of receipt only if it is pertinent to sample integrity, test method, or procedure.

Response: We disagree with the commenter. Recording the date and time of specimen receipt enables the laboratory to determine the elapsed time between specimen receipt and reporting of patient test results. It also provides a mechanism to monitor transportation times for specimens referred to the laboratory. Therefore, we are retaining this requirement formerly at § 493.1107(b) (now at § 493.1242(b)).

Comment: One commenter stated the final rule with comment period did not require a person's name or unique identifier on the test report.

Response: We agree with the commenter that the final rule with comment period did not specifically require a patient's name or unique identifier as part of the test report formerly at § 493.1109. Therefore, we are adding at § 493.1291(c)(1), a requirement for the laboratory report to include the patient's name with an identification number, or a unique patient identifier and identification number to ensure positive patient identification. The patient's name alone is not a unique identifier, and when used on the test report, the patient's name must be accompanied by an identification or accession number. When a patient's name is not used for confidentiality purposes, or when the identity of the person is not known, a unique patient identifier must be submitted with the specimen. The laboratory must also use an identification number. In reviewing the report requirements formerly at § 493.1109(b), interpretation was omitted. Therefore, we are adding interpretation to the test report requirements at § 493.1291(c)(6) for those test results that require supplemental information.

Comment: Some commenters disagreed with requiring the name and address of the laboratory performing the test on the test report. They believed that too much information would make the report crowded and confusing. Another comment received from a professional organization acknowledged the benefit of this requirement, but stated its application to cumulative reports causes disruption of data presentation and utility of the report and, in some cases, the information cannot reasonably be included.

Response: We agree the name and address of the laboratory performing the test is an essential piece of information that must be included on the test report. It provides a contact for the individual who requested or is using the test results when additional information is needed for result interpretation and patient care. If a laboratory determines its reports are crowded or confusing, it has complete latitude and responsibility to reorganize the report in a manner that will correct the problem as specified formerly at § 493.1703 (now at § 493.1299). A laboratory that generates cumulative reports may use a single character identifier (for example, an asterisk or subscript) to identify a particular reference laboratory that performed the test. This information (the name and address of the reference laboratory) may be defined on a subsequent page or on the back of the report. Laboratories may develop other formats to meet this requirement. However, we are retaining the requirement formerly at § 493.1109(b) (now at § 493.1291(c)(2)) to include the name and address of the laboratory where the test was performed.

Comment: One commenter questioned the appropriateness of maintaining test records in the patient's chart or medical record.

Response: The CLIA regulation does not preclude laboratories from storing test records in a patient's chart or medical record; however, records must include the following:

- Test analysis (including instrument printouts, if applicable).
- Identity of the personnel performing the test.

To retain this type of information in a patient's chart or medical record may be cumbersome and impractical for QA activities; however, it is at the discretion of the laboratory.

Comment: One commenter questioned whether computer records of reports are acceptable in lieu of paper files.

Response: The requirement formerly at § 493.1109(h) specifies that all test reports or an exact duplicate of each test report must be maintained by the laboratory in a manner that permits ready identification and timely accessibility. The information contained on the test report may be manually written, generated by an electronic system, maintained on microfilm, or any other means, provided it contains all of the information that was on the original test report. Therefore, we are deleting the reference to ''exact duplicate'' that was contained in the former § 493.1109(h), and amending the language now at § 493.1291(j) to clarify that the laboratory must be able to retrieve a copy of the original report. We are also making a conforming change in the retention requirement for test reports (now at § 493.1105(a)(6)).

Comment: Many commenters stated that the removal of the subpart on laboratory information systems (LIS) was inappropriate and not logical considering the current and future direction of collection and dissemination of laboratory data. Other commenters indicated that the current method of reporting patient results and the laboratory computer system was overlooked.

Response: We agree with all of the commenters and are addressing some of the commenters' concerns pertaining to electronic patient and testing information by doing the following:

- Adding a requirement at § 493.1101(e) for laboratories to store and maintain records in a manner that ensures proper preservation. Proper storage of patient records that are collected in a LIS is essential for record preservation and accurate recall of patient information. Without proper storage and maintenance of records, the timeframes, identification, and the accessibility of records will not be possible.
- Incorporating a requirement at § 493.1241(e) for laboratories using LIS to ensure that the requisition information is accurately transcribed or entered. The laboratory may establish its own mechanism to meet this requirement, possibly through random checks or representative sampling of LIS patient testing information verified against that submitted on the original test request.
- Adding a requirement at § 493.1291(a) that requires laboratories to ensure patient test results are accurately and reliably sent from the point of data entry to the final report's destination in a timely manner. We are providing frequently encountered reporting scenarios that must be reviewed by the laboratory to ensure the accuracy and reliability of the transmitted patient result information.
- Requiring at § 493.1291(c) that the date of the test report be identified on the report. This date must be maintained as the date testing results

were generated as a final report and must not change on copies reported at a later date.

The above requirements are intended to respond in part to the commenters' requests. We intend to publish, at a later date, a rule specific to laboratory information systems. For example, requirements for the establishment and verification of system programs, system security, system and device maintenance, system operator functions and responsibilities, and system backups.

Comment: One commenter was concerned about limited record storage space on-site and asked if off-site storage of records would be acceptable provided the laboratory was able to produce these records during an inspection.

Response: Records may be stored at a place of the laboratory's choosing providing the storage is appropriate and the laboratory can produce the documents within a reasonable time during the course of an inspection as required at § 493.1773(c).

Comment: Several commenters disagreed with the requirement to retain records for a minimum of 2 years or 5 years, depending upon the type of record. A professional organization questioned whether instrument printouts must be retained for 2 years if appropriate data are saved in a retrievable manner. Other commenters felt that 3 months, and, in one case, 6 months, would be sufficient time to retain instrument printouts.

Response: We believe all records related to testing, for example, records of test requests, patient test records including, if applicable, instrument printouts, and copies of test reports are essential for the ongoing QA reviews performed by the laboratory. Instrument printouts are test records and are sometimes used as test reports and for these reasons must be retained for the appropriate length of time unless all information is duplicated in another record system. Additionally, CLIA requires biennial certification that includes an inspection of the laboratory's activities for compliance with CLIA requirements by either an on-site inspection of the laboratory or a self-assessment inspection through use of the Alternate Quality Assessment Survey (AQAS). These inspections require a review of the testing performed by the laboratory since the previous biennial inspection. Two years is the minimum amount of time records must be retained to ensure that they are available for review at inspection. However, we are clarifying the record retention requirements for immunohematology and blood and blood products formerly at § 493.1107 introductory text and § 493.1221 (now at § 493.1105(a)(3)(ii)) and formerly at § 493.1109 introductory text (now at § 493.1105(a)(6)(i)) to ensure consistency with the FDA requirements for these types of records.

Subpart K—Quality Control for Tests of Moderate Complexity (Including the Subcategory), High Complexity, or Any Combination of These Tests

In the final rule with comment period, the QC rules are located in subpart K and include the general QC requirements and specific QC requirements for each specialty and subspecialty of testing. A phase-in period provided less stringent general QC requirements for unmodified moderate complexity tests approved by the FDA through the premarket notification 510(k) or premarket approval (PMA) process.

Following publication of the final rule with comment period, we received approximately 1,030 comments. Of these comments, 280 were directed at the general QC requirements, 67 pertained to the specialty and subspecialty QC requirements, and approximately 680 pertained to cytology and histopathology requirements. The majority of the comments disagreed with some portion of the requirements, indicating that the final rule with comment period was either too restrictive or too lenient. Some commenters requested clarification of certain requirements, while others offered specific revised language. A few comments agreed with the final rule with comment period, while others indicated the requirements had either been misinterpreted or misread. We addressed some of the commenters' issues in a technical correction published on January 19, 1993 in the **Federal Register** (58 FR 5215).

In evaluating the comments and considering the types of revisions to make in this subpart, we obtained recommendations from the CLIAC and consulted with various professional organizations and laboratory personnel. In September 1996, we participated in public discussions at a 2-day meeting in Atlanta, Georgia. At the public meeting, manufacturers, laboratory organizations, and State representatives made presentations concerning QC principles, control materials and systems, manufacturers' recommendations, costs associated with control testing, and personnel implications. Their recommendation was to make changes to accommodate new technology. Our changes in this final rule are based on the advice and comments we received.

Specific comments and response to comments regarding subpart K are set forth below.

Comment: We received mixed comments concerning the general QC requirements. Some commenters felt the QC requirements were burdensome and would increase the cost of testing and asked that these requirements be deleted or revised. Conversely, some commenters agreed with the requirements, indicating that QC is absolutely essential to producing accurate test results and is good laboratory practice. Others stated the requirements of subpart K were both reasonable and attainable. A few commenters requested further clarification.

Response: We agree with the comments that QC procedures are essential to good laboratory practice and production of accurate test results. Control procedures verify that the patient results are substantially unaffected by day-to-day variation caused by the test system, environment, or operator. While the requirement for implementing QC may initially increase the cost of testing in some settings, it may decrease the long term cost as improved accuracy and reliability of testing reduces the need for retesting and unnecessary procedures or treatments.

Comment: A manufacturer's organization requested that § 493.1202(c) be revised to include those products not subject to the FDA clearance process to allow laboratories performing these tests to meet the phase-in QC requirements.

Response: We agree that the regulation needs to be revised to include these products, and provisions addressing these products were added in the revisions to the regulations published in the January 19, 1993 technical corrections (58 FR 5215). Since these products are not evaluated by the FDA, they could not be included under § 493.1202(c) but were added to § 493.1202(b) and subject to all applicable standards of subpart K.

Comment: Comments were divided concerning the phase-in of the general QC requirements. Some commenters agreed with the phase-in while others were opposed. Some commenters felt that following manufacturers' instructions should be sufficient to meet the CLIA QC requirements. Others expressed concern that FDA would not complete the review and approval of manufacturers' QC instructions by September 1, 1994. Most commenters opposed the phase-in provision. Some

commenters were concerned that manufacturers' QC protocols cleared by the FDA might be less stringent than the CLIA QC requirements. Other commenters disagreed with having two sets of general QC requirements, and other commenters were confused about the phase-in requirements and requested clarification.

Response: We implemented a phase-in of the general QC requirements to allow previously unregulated laboratories performing only FDA-approved or cleared, unmodified, and moderate complexity testing sufficient time to implement effective QC programs. During the phase-in, the FDA was to establish a process to review and clear manufacturers' QC instructions for CLIA QC purposes. Under this process, laboratories could meet certain CLIA QC requirements by following the FDA-approved manufacturers' QC instructions. On four occasions, we extended the phase-in of the general QC requirements that are currently in effect until December 31, 2002. However, because the CLIA program is user fee funded, we decided it would be prudent to wait until the phase-in period ended before implementing the FDA QC review. This afforded us the survey experience necessary to determine whether an additional FDA review would be of benefit to laboratories. We realized through our experience inspecting laboratories that an additional FDA review would not be of such benefit. Therefore, in this final rule, we are eliminating the phase-in requirements and establishing minimum general quality system requirements applicable to all nonwaived testing, regardless of complexity. In addition, we are removing all references to the FDA QC clearance process that was not implemented. However, we agree with the commenters that it is essential for laboratories to perform testing according to the manufacturers' test system instructions as required formerly at § 493.1202(c)(1) (now at § 493.1252(a)).

Comment: A few comments were received in response to the environmental and safety requirements at § 493.1204. Some commenters indicated that the requirements were too lenient. Others were opposed to exempting moderate complexity testing from the requirements at § 493.1204 during the phase-in, stating that all laboratories should be subject to these requirements.

Response: We agree with the commenters and therefore are retaining the requirement formerly at § 493.1204 (now at § 493.1101, subpart J) and applying it to both moderate and high complexity testing. In addition, we are providing some flexibility to the requirement formerly at § 493.1204(b) (now at § 493.1101(d)) that requires laboratories to post safety precautions. The revisions now require that safety procedures be accessible rather than posted.

Comment: We received several comments concerning the requirements at § 493.1205. Most commenters opposed the requirement prohibiting the use of expired reagents. One commenter requested clarification of § 493.1205(c)(1) that requires the laboratory to define criteria for reagent and specimen storage conditions.

Response: We understand the concerns expressed regarding the use of rare and expensive reagents and materials beyond their expiration dates. However, the manufacturer has the responsibility for establishing expiration dates that ensure the reagents and materials will perform properly when used for patient testing. In addition, any changes in the labeling of *in-vitro* diagnostics must comply with Food, Drug, and Cosmetic Act requirements. Therefore, we are not making any revisions to the requirement formerly at § 493.1205(e)(1) (now at § 493.1252(d)) prohibiting the use of expired reagents and other materials.

In regard to licensed biological and blood products, any exceptions to dating requirements must be granted by the FDA in the form of an amendment to the product license. In this final rule, we are consolidating all requirements pertaining to the immunohematological testing and distribution of blood and blood products (now at § 493.1271(b)).

We are adding language to the requirement formerly at § 493.1205(c)(1) to clarify how the laboratory establishes and uses its criteria for storing reagents and patient specimens. The requirement now at § 493.1252(b), states that the laboratory must define criteria for those conditions in the manufacturer's test system instructions, when available, that are essential for proper storage of reagents and specimens, and accurate and reliable test system operation and test result reporting. The criteria must be consistent with the manufacturers' instructions, if provided. These conditions must be monitored, documented, and include (1) water quality; (2) temperature; (3) humidity; and (4) electrical tolerances.

Comment: One commenter agreed with the requirements at § 493.1211, Procedure manual. Another commenter suggested that the procedure manual requirements be deleted. Two commenters opposed permitting the use of the manufacturer's package insert to satisfy the requirements at §§ 493.1211(b)(1) through 493.1211(b)(13). Another commenter suggested that laboratories be required to retain each procedure's original specifications and instructions for use as provided by the manufacturer, and maintain a list of any alterations or changes in the procedure manual.

Response: We disagree with the commenter who requested that the procedure manual requirements be deleted. All laboratories must maintain and follow procedure manual instructions in order to provide uniform patient testing. Therefore, we are retaining the requirements for a procedure manual now at § 493.1251. Laboratories may use the manufacturer's test system instructions to meet many of the procedure manual requirements, but must supplement them with any laboratory-specific information related to its testing and reporting practices. Examples are the laboratory's procedures for reporting patient test results, including panic values or alert values, corrective actions to follow when test systems become inoperable, and criteria for specimen referral. The use of the manufacturer's test system instructions to meet many of the procedure manual requirements is permitted to ensure that laboratories follow the manufacturer's instructions for patient testing and to minimize the burden on laboratories in developing procedure manuals.

For clarity and consistency, we are reiterating the requirements formerly at §§ 493.1103(a) and 493.1211(b)(14) (now at §§ 493.1242 and 493.1251) that the laboratory have written policies and procedures for specimen submission. In addition, we included language now at § 493.1251(b)(13) to clarify the use of laboratory information systems for entering patient test results.

In addition, we agree with the commenter that laboratories must have copies of test procedures. Therefore, we are retaining the requirement now at § 493.1251(e) that laboratories must maintain a copy of the procedure with the dates of initial use and discontinuance for 2 years after a procedure is no longer used.

Comment: Several commenters opposed the requirement at § 493.1211 for the director to approve, date, and sign the procedure manual, approve any change in procedure, or re-approve the manual should there be a change in directorship. One commenter suggested that the requirement be revised to state each procedure must be approved by the director before patient testing.

Response: The director is the individual ultimately responsible for the operation and administration of the

testing facility and is therefore responsible for authorizing all testing procedures and any alterations or revisions of these procedures. If a change in directorship occurs, re-approval of the manuals by the new director is necessary since he or she assumes responsibility for all testing procedures and any alterations or revisions of the procedures. We agree with the comment stating that each procedure should be approved by the director before patient testing. Therefore, we are revising the requirement formerly at § 493.1211(d) (now at § 493.1251(d)) to specify that the director reviews each procedure and change in procedure before use. We are also emphasizing that we do not expect laboratories to suspend testing for those procedures already in use that may not have been approved before patient testing. However, effective April 24, 2003, all alterations in current procedures and all newly implemented procedures must be reviewed and signed by the director before use.

In addition, we are revising the requirement formerly at § 493.1211(e) (now at § 493.1251(d)) to include the provision that requires procedures to be re-approved if the directorship changes. Section 493.1251(d) now states, ''procedures and changes in procedures must be approved, signed, and dated by the current laboratory director before use.'' If the directorship changes, the current director would not be expected to suspend testing to review the procedures in use or changes to procedures approved by the previous director. However, the current director must review all procedures in use by the laboratory in a timely manner.

Comment: Approximately one third of the comments received disagreed with § 493.1213, Establishment and verification of method performance specifications. Some individuals opposed verifying the manufacturer's performance specifications for those methods cleared by FDA as meeting certain CLIA requirements for QC. One commenter disagreed with the requirement to establish performance specifications for those methods developed in-house, modified by the laboratory, or not cleared by FDA as meeting certain CLIA QC requirements. Another individual suggested that the standard be retroactive and apply to all test methods. One commenter asked that this standard be revised to state, ''The provisions of this section are not retroactive for previously unregulated laboratories. Previously unregulated laboratories are not required * * *.''

Response: We understand the commenters' concerns about the time and resources necessary to establish or verify performance specifications. However, these requirements ensure that the laboratory has either established test system performance specifications or verified that it can obtain the manufacturer's performance specifications in the laboratory's environment using the laboratory's testing personnel. In addition, establishment or verification of performance specifications are integral to the laboratory's establishment of appropriate and effective QC and calibration protocols. These protocols must include descriptions of the numbers, types, and concentrations of all calibration and control materials, as well as the performance intervals. Calibration and control protocols based on unverified performance specifications could result in poorly controlled and inaccurate testing. In the interest of establishing appropriate calibration and control practices and improving the reliability, accuracy, and usefulness of patient testing, we are retaining the requirements formerly at § 493.1213, and are now applying them to nonwaived testing at § 493.1253.

Laboratories employing methods (not modified by the laboratory) that have manufacturer-established performance specifications must demonstrate before reporting patient test results that they can obtain performance specifications for accuracy, precision, and reportable range of test results for the test system, comparable to those established by the manufacturer. The laboratory director must decide the extent to which these performance specifications are verified based on the method, testing conditions, and personnel performing the test.

In addition, we are clarifying when a laboratory must establish test system performance specifications (for example, laboratories using a test system in which the manufacturer does not provide performance specifications) now at § 493.1253(b)(2). Laboratories must, before reporting patient test results, establish, as applicable, performance specifications for the following performance characteristics: (1) Accuracy; (2) precision; (3) analytical sensitivity; (4) analytical specificity, including interfering substances; (5) reportable range of test results for the test system; (6) reference intervals (normal ranges); and (7) any other performance characteristic required for test performance.

Section 493.1253(b)(1) uses the term ''FDA-cleared or approved test system'' as defined (at § 493.2, Definition) in the November 9, 1997 revisions to the Food, Drug and Cosmetic Act (Pub. L. 105–115), to mean a test system cleared or approved by the FDA through either the premarket notification (510(k)) or premarket approval (PMA) process for *in-vitro* diagnostic use. This includes test systems exempt from FDA premarket clearance or approval.

Regulations do not have retroactive effect. The CLIA requirement's effective date became applicable to newly regulated laboratories on September 1, 1992. Those laboratories that were subject to regulations prior to this September 1, 1992 effective date were already required to validate test procedures under former Federal regulations before the CLIA requirements were implemented. This rule does not have a retroactive effect. Laboratories performing unmodified moderate complexity tests cleared or approved by the FDA are not required to retroactively verify the manufacturer's performance specifications. The results of the laboratory's control procedures, proficiency testing (required under subpart H) and assessment activities are used to verify test performance. However, as of April 24, 2003, laboratories must, before testing, either verify or establish performance specifications for any new test system.

Comment: Some commenters expressed approval of the requirements for the establishment and verification of a test system's method performance specifications before its use, and maintaining records of this activity while the test system is used for patient testing.

Response: We accept these positive comments and are retaining the requirements for the establishment and verification of method performance specifications formerly at § 493.1213 (now at § 493.1253). However, we realize the QC record retention requirements formerly at § 493.1221 may have been misinterpreted as permitting the laboratory to discard method performance specification records after a 2-year period even though the method may have continued to be used beyond this timeframe. Therefore, the analytic systems record retention requirement formerly at § 493.1221 (now at § 493.1105(a)(3)(i)) specifies that records of the laboratory's establishment and verification of method performance specifications must be retained for the period of time the test system is in use by the laboratory, but not less than 2 years. In addition, we are revising the original QC record retention requirement to accommodate the reorganization of the regulation and clarify its intent.

Comment: A few commenters disagreed in general with the

requirements at § 493.1215, Equipment maintenance and function checks. Other commenters requested clarification. One commenter felt that the requirements were too stringent, and another offered specific language for revision. One commenter felt CMS, not the manufacturer, should establish the frequency for performing function checks.

Response: Equipment maintenance and function checks are necessary to ensure accurate and reliable test performance. We are relocating the requirement formerly at § 493.1215 (now at § 493.1254) and renaming it Maintenance and function checks. Laboratories using unmodified manufacturers' equipment, instruments, or test systems must perform maintenance and function checks as defined by the manufacturer with at least the frequency specified by the manufacturer. Laboratories must also document maintenance and function checks performed. We are adding language at § 493.1254(a)(2) requiring that function checks be within the manufacturer's established limits before conducting patient testing. We are also retaining the present requirement (now at § 493.1254(b)) for laboratories to establish protocols that ensure proper test system performance, accurate and reliable test results and test reporting for equipment, instruments, or test systems developed in-house, commercially available but modified by the laboratory, or when protocols for maintenance and function checks are not provided by the manufacturer. In addition, laboratories must document the maintenance and function checks performed.

Under this final rule, we are not defining intervals for the performance of maintenance or function checks because the manufacturer is better able to define the appropriate procedures and intervals necessary to maintain and ensure proper equipment, instrument, and test system performance.

Comment: Several commenters suggested that § 493.1217, calibration and calibration verification, or substantially equivalent requirements, should also apply to FDA-approved or cleared, unmodified moderate complexity testing at § 493.1202(c). In addition, we received comments requesting clarification of § 493.1217. One commenter stated that CMS, not the manufacturer, should establish the frequency of calibration. A manufacturer commented that a loose interpretation of the calibration verification requirement to assay calibration materials in the same manner as patient samples is needed for certain blood gas analytes because buffers and gases used to calibrate the instruments are not like patient samples and cannot be assayed in the same manner as patient samples.

Response: We agree with the commenters and are specifying in this final rule that effective, April 24, 2003, calibration and calibration verification requirements (now at § 493.1255) will apply to all nonwaived testing.

To respond to the commenters' concerns that the calibration and calibration verification requirements are unclear, we are making some minor revisions in language for clarification purposes and removing duplicate requirements. For example, the definitions of calibration and calibration verification and reportable range are being slightly modified (now at § 493.2). We are also removing the requirement formerly at § 493.1217(b)(2)(ii)(B)(1) for laboratories to perform calibration verification using calibration materials appropriate for the methodology and, if possible, traceable to a reference method or reference material of known value to allow laboratories flexibility in choosing materials for calibration verification.

In addition, we are retaining the requirement for laboratories, at a minimum, to perform calibration and calibration verification procedures using the manufacturers' test system instructions and the criteria verified or established by the laboratory formerly at §§ 493.1217(b)(1) and 493.1217(b)(2) (now at §§ 493.1255(a)(1), 493.1255(a)(2), 493.1255(b)(1) and 493.1255(b)(2)). We are also retaining the requirement that calibration must be performed whenever calibration verification procedures are unacceptable and calibration verification be performed using a minimum of 3 values to verify the laboratory's reportable range, at least once every 6 months or whenever an event occurs as specified formerly at § 493.1217(b)(2)(ii)(C) (now at § 493.1255(b)(3)).

In response to the comment that the frequency of calibration be mandated by CMS, we are retaining the requirement formerly at § 493.1217(b)(1) (now at § 493.1255(a)) that requires laboratories to calibrate according to the manufacturer's instructions, if provided, and the laboratory's specifications. We believe that laboratories should perform calibration at the interval specified by the manufacturer to ensure proper instrument and test system performance. For calibration verification formerly at § 493.1217(b)(2) (now at § 493.1255(b)), laboratories are to follow the manufacturer's specifications and the laboratory's established protocols for calibration verification that must be performed at least once every 6 months. We believe this is the maximum interval allowable for verifying accuracy and stability. In addition, we are emphasizing that these regulations set forth minimal requirements. In establishing or verifying performance specifications as required at § 493.1253, the laboratory may find it necessary to calibrate or verify calibration more frequently or to use more calibration materials than required at § 493.1255.

In response to the comment concerning the inability of testing calibration materials (buffers and gases) in the same manner as patient specimens when verifying the calibration of blood gas assays, we are retaining the additional requirements for routine chemistry formerly at § 493.1245 (now at § 493.1267) that supersede the general calibration and calibration requirements at § 493.1255. Section 493.1267(a) specifically addresses calibration and calibration verification of blood gas analyses and states the laboratory must calibrate or verify calibration according to the manufacturer's specifications and with at least the frequency recommended by the manufacturer. As long as the laboratory follows the manufacturer's calibration and calibration verification instructions for the blood gas instrument, the CLIA requirements for calibration and calibration verification are met.

Comment: We received many comments concerning various components of § 493.1218, Control procedures. Some commenters misread the CLIA regulation, and others offered specific language for revision. Most commenters opposed testing two levels of control material each day of use. One commenter indicated that the CLIA requirements are burdensome and will increase the cost of testing. Some commenters expressed concern that the requirements are arbitrary and do not recognize unit use test systems. Another commenter asked if procedural controls may be used to satisfy the control requirements.

Response: We appreciate the commenters' concerns about the frequency and costs of performing control testing. However, CLIA regulations will continue to describe the purpose of control procedures, that is, to assess the accuracy and precision of test performance. The control procedures must monitor the complete analytical process by detecting immediate errors (those that occur due to test system failure, adverse environmental conditions or operator performance problems) and monitor over time the accuracy and precision of test performance that can be influenced by

subtle changes in test system performance, environmental conditions, and variance in operator performance (for example, different operators and same operator variations in specimen handling and testing).

In response to the comments concerning unit use test systems and the use of procedural controls, we are making allowances for the use of procedural controls in Appendix C of the State Operations Manual (CMS Pub. 7) when equivalent quality procedures can be demonstrated.

In addition, we are providing a definition for test system (now at § 493.2). A test system is the instructions and all of the instrumentation, equipment, reagents, and/or supplies needed to perform an assay or examination and generate test results.

A control material must detect errors in the entire testing process. It must also monitor the quality of the results provided by the test system. It may be supplied by the test system manufacturer or another source. We are also relocating the requirement for control materials to be tested in the same manner as patient samples formerly at § 493.1218(c) (now at § 493.1256(d)(8)) and clarifying that this requirement applies to control materials and that over time control testing must be rotated among all operators who perform the testing (now at § 493.1256(d)(7)).

We are reducing the frequency of testing control materials from ''each run'' to ''each day of testing.'' We are retaining the former requirements for qualitative procedures (test positive and negative control materials) and quantitative procedures (test two levels of control material). For test procedures producing graded or titered results, we are relocating the requirement to test a negative control and a control of graded or titered reactivity from Syphilis serology and General immunology formerly at §§ 493.1239(b) and 493.1241(a), respectively (now at § 493.1256(d)(3)(iii)).

As part of updating the requirements for new technology and test methodologies formerly at § 493.1218(b)(3) (now § 493.1256(d)(5)), we are revising the wording of the control requirement for electrophoresis procedures.

Comment: One commenter urged that we remove specific stipulations for frequencies of performing QC or calibrations and substitute reference to an agency or professional association guidelines. The commenter also recommended that we accept alternate approaches suggested by a manufacturer as documented in test system instructions approved by the FDA. Another commenter suggested that § 493.1218(a) be revised to state, ''that the laboratory should run controls as specified by the manufacturer's instructions.'' Several commenters and one organization stated it is the laboratory director's responsibility to design the control system needed to achieve the desired quality.

Response: We consider the requirements established in subpart K as the minimum control measures needed to ensure accurate and reliable test results. According to the requirements formerly at § 493.1213 (now at § 493.1253), each laboratory must verify or establish a test system's method performance specifications and use this information in determining appropriate calibration and control protocols. This may include more frequent testing and greater numbers of materials than specifically provided under CLIA regulations. For example, the laboratory is required to perform calibration and control procedures in the manner necessary to ensure quality results. In cases where the manufacturer's instructions require more stringent testing of calibrators, control materials, or both, the laboratory is required to follow the manufacturer's instructions. Therefore, we are clarifying that laboratories must follow the manufacturer's instructions for control testing if they meet or exceed the requirements now at § 493.1256(d)(3).

We agree with the comment concerning the laboratory director's responsibility to determine appropriate control procedures to monitor the complete analytical process. This requirement is specified in CLIA regulations under the director's responsibilities at § 493.1407(e)(5) for moderate complexity testing and § 493.1445(e)(5) for high complexity testing.

Comment: A commenter suggested that acceptable control materials are two samples of different concentrations of controls or two concentrations of calibration material of a different lot other than the lot used for assay calibration, or any combination that results in both normal and abnormal values.

Response: We agree with the commenter and emphasize that any calibrator used as control material must be of a different lot number than the one(s) used to establish a cutoff value or calibrate the assay. Therefore, we are revising this requirement formerly at § 493.1218(b)(2)(now at § 493.1256(d)(9)) to clarify that the calibrators used as control materials must be of different concentrations than the calibrators employed to set instrumentation. We recommend that the acceptable range of control materials reflect some clinical decision points, both normal and abnormal.

Comment: One commenter suggested that § 493.1218(d) be revised to include a provision that if the performance specifications at § 493.1213 are exceeded, the laboratory must take corrective action before patient testing can continue.

Response: We agree with the commenter. The requirements formerly at § 493.1219(a) (now at § 493.1282(b)(1)) require corrective action, and the requirements formerly at § 493.1701 (now at § 493.1289(b)) require the laboratory to review the effectiveness of its corrective actions and, if necessary, revise policies and procedures to prevent recurring problems.

Comment: One commenter disagreed with the requirement to check each batch or shipment of media.

Response: The CLIA regulations allow laboratories to use the manufacturer's QC checks of certain media, provided the manufacturer's product insert specifies that the manufacturer's QC checks meet the NCCLS standards for media QC formerly at § 493.1218(f)(4), now addressed in Appendix C of the State Operations Manual (CMS Pub. 7). For media not included by NCCLS, we believe it is critical that the laboratory check each batch of media to ensure that it is not contaminated, supports growth of appropriate organisms, and elicits the correct biochemical response(s). The former § 493.1218(f)(4) (now § 493.1256(e)(4)) clarifies that media checks must be performed before, or concurrent with, initial use of media.

Comment: A few commenters expressed disagreement with the requirement to evaluate the detection phase of direct antigen systems and the extraction phase when it is included.

Response: We believe the laboratory must verify that all steps of a testing procedure are functioning properly to prevent erroneous results. Therefore, we are retaining the requirement formerly at § 493.1218(b)(4) (now at § 493.1256(d)(3)(iv)) that requires laboratories to test two control materials, one that is capable of detecting errors in the extraction phase.

Comment: One commenter agreed with requiring the determination of statistical parameters for each lot of calibration or control materials.

Response: We are retaining the requirement formerly at § 493.1218(d)(2) (now at § 493.1256(d)(10)(i)) for laboratories to have statistical

parameters for each lot of control material. In addition, we are clarifying that the requirement applies to controls with quantitative results. When calibration materials (not used to establish a cutoff value or calibrate the test system) are used as control materials, the laboratory must have statistical parameters for each lot of calibration material.

Comment: Some comments received were in reference to § 493.1219, Remedial actions. One commenter requested clarification and another requested deletion of § 493.1219(a)(2) that requires the laboratory to document all remedial action taken when patient test results are outside of the laboratory's reportable range for the test system. One individual asked for clarification of § 493.1219(d)(3) that requires the laboratory to maintain exact duplicates of both original and corrected reports for 2 years when errors in the reported test results are detected. One commenter suggested that no patient results that are less than the lowest calibrator or higher than the highest calibrator can be reported unless they are reported as less than or greater than the lowest or highest calibrator or the patient specimen is diluted to determine a higher value.

Response: The requirement formerly at § 493.1219(a)(2) (now at § 493.1282(b)(1)(ii)) requires documentation of all remedial actions (now ''corrective'' actions) when patient values are outside of the laboratory's reportable range of patient test results. The documentation can be an instrument printout or other document that reflects the problem, corrective action, and outcome. The laboratories must retain this information for the required period and the corrective actions themselves may be as elementary as diluting and retesting the specimen. We are not making any revisions to this requirement.

The requirement formerly at § 493.1219(d)(3) (now at § 493.1105(a)(6)) requires the laboratory to maintain a copy of the original report, or be able to retrieve a copy of the original report and the corrected report for 2 years. Copies of test reports may be manually written, photocopies, electronically generated, or maintained on microfilm provided they contain all of the information supplied on the original test record or report.

We agree with the suggestion that results outside of the reportable range of the test system may not be reported without corrective action or explanatory remarks. Therefore, requirements formerly at § 493.1219 (now at § 493.1282, Corrective actions) require laboratories to have corrective action policies and procedures that are followed as necessary to maintain the laboratory's operation for testing patient specimens in a manner that ensures accurate and reliable patient test results and reports. This includes policies governing the reporting of patient results that exceed the reportable range of the test system. The analytic assessment requirements at § 493.1289 require the laboratory to monitor and evaluate the corrective actions taken and revise policies and procedures as necessary to prevent recurrences of problems.

Comment: One commenter suggested that CLIA rules require all original worksheets and instrument printouts to be retained for 6 months, indicating that some laboratories destroy, delete, or erase records of unacceptable QC in order to avoid showing remedial action and reassessment of all patient tests results associated with the failure.

Response: We understand the concerns expressed by the commenter. However, we believe the CLIA regulations adequately address documenting all control procedures performed formerly at § 493.1221 (now at §§ 493.1256(g) and 493.1105(a)(3)), maintaining records of all control procedures performed formerly at § 493.1221 (now § 493.1105(a)(3)), assessing corrective actions taken formerly at § 493.1705 (now at §§ 493.1289(a) and (b)) and retention of the original worksheets and instrument printouts for a period of 2 years or more formerly at § 493.1107 (now at § 493.1105(a)(3)). We also believe that if the laboratory deletes or alters a control result in any manner, it is expected that the laboratory will document the exact circumstances in which deletion or alteration occurred and document all corrective actions taken to prevent reoccurrence.

Comment: One commenter felt that there should be a requirement that any abnormal, life-threatening, or panic value result obtained on a moderate complexity test should be repeated by a more accurate method of testing.

Response: The requirement formerly at § 493.1109(f) (now at § 493.1251(b)(13)) requires laboratories to develop written procedures for reporting life-threatening results (panic or alert values). In addition, under the requirement formerly at § 493.1109(f) (now § 493.1291(g)) laboratories must immediately alert the individual or entity that requested the test and, if applicable, the individual responsible for using the test results when any test result indicates an imminently life-threatening condition. In addition, it is the responsibility of each laboratory to ensure that the results it reports are accurate. Repeat testing is one method of verifying the test results. However, it is up to each laboratory to determine the protocols it will follow to confirm the test results that it reports.

Section 493.1223 Condition: Quality Control-Specialties and Subspecialtes for Tests of Moderate or High Complexity, or Both

Specific comments received and response to comments regarding § 493.1223, specialty or subspecialty control requirements are set forth below.

Comment: One commenter stated that the specialty and subspecialty QC requirements are too lenient.

Response: The specialty and subspecialty QC requirements are minimum requirements that reflect good laboratory practice and must be followed by all laboratories performing nonwaived testing. However, based on the laboratory's establishment and verification of its test systems' performance specifications (now at § 493.1253), the laboratory may determine that, to ensure accurate and reliable test results, it must implement more stringent control procedures than the minimum requirements imposed. In addition, it is the laboratory director's responsibilities to ensure that the laboratory has systems that ensure the quality of the laboratory services provided and identify failures in quality as they occur (§§ 493.1407(e)(5) and 493.1445(e)(5)).

Comment: One commenter disagreed with § 493.1223 stating a laboratory could lose approval to perform testing in an entire specialty or subspecialty if it is deficient in performing QC for a single test. The commenter urged that the language be changed to ''Failure to satisfy requirements for an individual test or analyte would result in loss of approval for that test or analyte only.''

Response: We emphasize that CLIA certification of laboratories is not granted on a test-by-test basis, but by specialty or subspecialty of testing. Therefore, if a laboratory has significant problems related to only one test or analyte in a specialty or subspecialty and the laboratory fails to correct those problems, it could jeopardize its certification for the specialty or subspecialty area. For example, the laboratory is notified in writing of the deficiencies found during a survey and is given an opportunity to correct the deficiencies. If the laboratory does not correct the deficiencies, sanctions could be imposed as specified in Subpart R—Enforcement Procedures. Therefore, we are deleting the enforcement

information formerly at § 493.1223 because subpart R contains this information. In addition, revocation of specialty or subspecialty certification for problems related to a particular test would be taken only as a last resort.

Sections 493.1225 Condition: Microbiology; 493.1227 Condition: Bacteriology; 493.1229 Condition: Mycobacteriology; 493.1231 Condition: Mycology; 493.1233 Condition: Parasitology; and 493.1235 Condition: Virology

Specific comments received and response to comments regarding §§ 493.1225, 493.1227, 493.1229, 493.1231, 493.1233, and 493.1235 are set forth below.

Comment: A professional organization, the American Society for Microbiology (ASM), commented that the CLIA QC requirements should be revised over time as new information is made available about the performance parameters of reagents or test systems. At a CLIAC meeting, this organization presented data on control failures for commercial microbiology reagents and stains and suggested that the current frequencies for control testing of a number of microbiology tests or reagents are excessive. ASM collected the data via two surveys of 304 clinical microbiology laboratories that perform varying levels of microbiological testing. It included failure rates for a total of 14,731 lots of reagents and stains, representing 21 different tests. Reagents and stains for 11 of the tests surveyed currently have control testing frequencies specified in the CLIA regulations: catalase, oxidase, coagulase plasma, *Salmonella* antisera, *Shigella* antisera, Gram stain reagents, optochin, bacitracin, Cefinase™ (beta lactamase), X and V factor strips and disks, and germ tube test. In this final rule, specific control testing frequencies are not given for eight reagents (spot indole, staphylococcal latex reagents, streptococcal latex grouping reagents, PYR disks, deoxycholate, KOH (fungal), LAP disks, and ALA) and two stains (lactophenol cotton blue and methylene blue). Based on the results of their surveys, the ASM proposed that laboratories should only be required to test new lot numbers of those commercial microbiology reagents that had a 98 percent or greater success rate (all reagents they surveyed met this requirement). In addition to testing each new lot, ASM recommended that laboratories test *Salmonella* and *Shigella* antisera every 6 months thereafter. ASM recommended that for epidemiological testing conducted in public health laboratories, the frequency for testing Salmonella and Shigella antisera should be determined by the periodicity supported by each laboratory's data.

In making this presentation, ASM stated that the changes they were proposing would improve the cost effectiveness of the CLIA program and quality assurance programs in clinical laboratories without compromising public health. The CLIAC supported the proposal and recommended the incorporation of these changes into the CLIA regulations.

Response: We appreciate the efforts of ASM, and the data they provided. The survey results provided the supporting information and data needed to revise the control testing frequency requirements. Based on the low failure rates for the commercial microbiology reagents surveyed, we agree it is adequate to test the majority of these reagents with each batch (prepared in-house), lot number (commercially prepared), and shipment when prepared or opened for positive, negative, and graded reactivity, as applicable. We also agree with checking antisera initially and once every 6 months thereafter except for epidemiological testing that is not subject to CLIA.

For two of the stains surveyed, the Gram stain and methylene blue, we do not agree that the low failure rate of the reagents is sufficient reason to decrease the stringency of the control requirements. The Gram stain procedure uses several reagents and has multiple steps that require specific timing for accurate results. Also, interpretation of the stained smear requires individual skill and expertise. By decreasing the frequency of control testing for this procedure to once every batch, lot number, and shipment, small laboratories that perform only rare Gram stains on direct specimens may not test controls for a period of months. We do not believe this is appropriate for a critical test used, in some cases, to presumptively diagnose an infectious disease (for example, direct smear for *Neisseria gonorrhoeae*). For this reason, we are maintaining the current weekly control testing requirement for Gram stain in addition to testing with each new batch, lot number and shipment.

Similar to the Gram stain usage in small laboratories, methylene blue stains may not be performed for an extended period of time, especially in laboratories that do not routinely use this staining procedure. We do not believe it is overly burdensome to require control testing of this stain each day of use.

In making the revisions discussed above, we deleted the specific control requirements for the reagents surveyed by ASM in the subspecialties of bacteriology formerly at § 493.1227 (now at § 493.1261) and mycology formerly at § 493.1231 (now at § 493.1263), except for requiring in bacteriology that the Gram stain be tested each week of use, and antisera be tested when each batch, lot number, and shipment is prepared or opened, and once every 6 months thereafter. We are also requiring in mycology that the laboratory check each batch, lot number, and shipment of lactophenol cotton blue when prepared or opened for intended reactivity with control organisms. Additional control testing for lactophenol cotton blue is not required. The required control testing frequencies for other reagents and stains will default to the general control procedures requirements formerly at § 493.1218(f) (now at § 493.1256(e)(1) and (2)). The general control requirements for reagents include testing each batch (prepared in-house), lot number (commercially prepared) and shipment when prepared or opened. The general control requirements for stains (for example, methylene blue) include testing staining materials for intended reactivity each day of use. As indicated by ASM, we believe these changes will decrease the cost of microbiology testing, without significantly affecting the quality of the test results.

The CLIAC requested further input from ASM on appropriate control requirements for microbiology. ASM submitted the following recommendations based on consultation with clinical microbiologists:

- The mycology requirement (for auxanographic media for nitrate assimilation) to check the nitrate reagent each day of use with a peptone control is not relevant since most laboratories no longer perform this test for fungal identification. This requirement could be deleted, and if laboratories do use the procedure, it would be sufficient to perform control testing with each batch or lot.
- The requirement for parasitology laboratories to check permanent stains, each month of use, with a fecal sample should be changed to ''with a fecal sample or commercial QC slide.''
- To control the decontamination process for mycobacteriology culture specimens, process a specimen containing *Mycobacterium fortuitum* with each new lot number or batch of decontaminating agent.
- The frequency of control testing should be standardized for all microbiology subspecialties. Although there has been no data collected for reagents or stains used in subspecialties

other than bacteriology, ASM suggested that it was their experience that these reagents and stains perform as well as the reagents surveyed for bacteriology.

- Molecular amplification control procedures should adhere to standards outlined in the NCCLS document ''Molecular Diagnostic Methods for Infectious Diseases, MM3–A, 1995.'' At a minimum, control procedures for these tests should validate cell lysis, absence of inhibitors, absence of contamination, and adequate amplification. The following controls should be included with each run:
- Positive control (low range of assay sensitivity).
- One to five negative controls.
- Internal control.
- Quantitative assays should include two to three standards of known copy number. For microbial genotyping, control procedures should include at least two isolates of the same species being tested. One isolate should have the same phenotype as the unknown, and one should be a different phenotype.

Response: Our responses to the above recommendations are set forth below.

We agree that the mycology requirement for control testing of nitrate assimilation on auxanographic media is not relevant for the large majority of laboratories performing fungal identification, and have deleted that requirement. If laboratories use the procedure, they will be required, as stated formerly at § 493.1218(f) (now at § 493.1256(e)(1)) to test the medium and reagents with each batch (prepared in-house), lot number (commercially prepared), and shipment when prepared or opened. This will be the same control testing as required for other reagents and media used for fungal identification procedures.

The language formerly at § 493.1233(c) (now at § 493.1264(c)) requires laboratories to check permanent stains each month of use by using a fecal sample control. This terminology does not preclude the use of a fecal sample as a control or a commercially prepared control slide. The requirement remains as written in existing CLIA regulations; however, we will note this clarification in Appendix C of the State Operations Manual (CMS Pub. 7).

We recognize ASM's concern that the mycobacteriology decontamination process be monitored and adequately controlled to ensure that the decontaminating agent is of the proper strength to kill contaminating organisms without destroying mycobacteria (especially *Mycobacterium tuberculosis*). However, the method they suggested for doing this is only one way in which it may be accomplished. There are a number of other ways in which this process may be controlled (for example, monitoring the contamination rate over time to ensure the appropriate organisms are being killed). In an effort to maintain flexibility in CLIA regulations, in this final rule, we are not adding this ASM proposed control requirement to those for mycobacteriology. As noted formerly at § 493.1103(a) (now at § 493.1232), the laboratory must establish and follow written policies and procedures that assure optimum integrity of patient specimens from the time they are collected until testing has been completed and results reported. In addition, former § 493.1103(a) (now at § 493.1242(a)(6)) requires laboratories to have and follow written policies and procedures for specimen processing, and former § 493.1703 (now at §§ 493.1249(a) and (b)) requires the monitoring and assessment of these policies and procedures, and the implementation of corrective actions to resolve problems that are identified. These requirements ensure that the processing of mycobacterial specimens is monitored, assessed, and controlled, while allowing the laboratory to use any of several acceptable methods to do so.

We agree with ASM that, whenever possible, the frequency for control testing should be standardized for all microbiology subspecialties. Frequencies for individual reagents and stains are not specified in CLIA regulation for mycology and virology. For parasitology, a frequency requirement (to test once a month) is only given for permanent stains. The frequency requirement for all other reagents and stains in these subspecialties is the default contained in the general control procedure requirements that are now at § 493.1256(e)(1) and (2).

We agree appropriate requirements for molecular amplification procedures are needed, and that the NCCLS standards are an excellent reference for laboratories to use. Requirements addressing most of the recommendations made by ASM for amplification procedures are included in CLIA regulations, although not as specifically as suggested by this organization. CLIA regulations require the laboratory director to have control procedures to monitor the complete analytic process. For amplification procedures this includes, in general, validating cell lysis and ensuring absence of inhibitors, absence of contamination, and adequate amplification. The CLIA requirements for control procedures for all tests are now at § 493.1256(d). This provision requires all laboratories to follow manufacturer's instructions for control testing, and to, at minimum, conduct a test that includes two control materials of different concentrations (a positive and negative control are required for qualitative tests) on each day patient specimens are tested. CLIA regulations require that if the laboratory determines additional numbers or types of controls, or a greater frequency of running controls is needed to detect immediate error and monitor test performance over time, the numbers, types, and or frequency of controls must be increased accordingly.

While we agree with the recommendation made by ASM describing the positive and negative controls that should be used for molecular amplification procedures, the CLIA control requirements are minimum requirements and do not specify that a positive control must be at the low range of assay sensitivity, or that more than one negative control be tested daily. Likewise, these minimum requirements do not specify the types of controls that must be included with microbial genotyping, but only that two controls must be tested each day patient specimens are tested.

However, if test system instructions specify such control testing, or if the laboratory determines (during its initial evaluation of the test system at § 493.1253) that more controls are needed, the additional control testing must be performed.

For molecular amplification procedures, ASM also recommended the inclusion of an internal control in each run, primarily to detect inhibition of the amplification process. We agree that for some amplification procedures the presence of inhibitors or interfering substances in certain specimens may cause false negative test results, and that for these procedures, a control system is necessary to detect inhibition. However, as noted by NCCLS, inhibitors are not a significant source of false negative results for every test, and if inhibitors or interfering substances are encountered only rarely, NCCLS does not recommend running controls for inhibition. Therefore, we have added a requirement at § 493.1256(d)(3)(v) that states, if reaction inhibition is a significant source of false negative results, the laboratory must include a control system to detect such inhibition.

In response to the ASM recommendation that quantitative assays include two to three standards of known copy number, as stated above, under CLIA regulations, quantitative

tests must include at least two control materials of different concentrations per day. Standards may be used in lieu of control materials, as long as they are not the same as the materials used to calibrate the test system or establish a cutoff.

In reviewing the CLIA regulations concerning control procedures and QA requirements for molecular amplification procedures, the CLIAC discussed appropriate control procedures and QA for genetic testing (September 16, 1998 through September 17, 1998). CLIAC recommended that controls for genetic testing should be considered for laboratories in general, including ensuring that adequate controls are in place to minimize contamination. This is especially important when performing molecular amplification procedures. To ensure the control of contamination, we have amended the requirements for facilities, formerly at § 493.1204(a) (now at § 493.1101(a)) to require laboratories to be constructed, arranged, and maintained to minimize contamination of patient specimens, equipment, instruments, reagents, materials, and supplies. A uni-directional workflow must be maintained for molecular amplification procedures not contained in closed systems. This must include physically separate areas for specimen preparation, amplification and product detection and, as applicable, reagent preparation. We believe these measures will decrease the potential for contamination to the extent possible in a clinical laboratory.

Comment: Several commenters requested clarification of the control requirements for kit systems used for bacterial and fungal identification. One commenter specifically requested the addition of a provision at § 493.1231, Mycology, that would require the testing of each new shipment of test kits or strips used for organism identification with organisms giving positive and negative reactions for each test before or concurrent with testing of clinical isolates. Another commenter questioned whether these systems would be subject to the requirement described at § 493.1202(c)(4) to test at least two levels of control materials each day of testing.

Response: We agree with the commenter that in mycology, or any other subspecialty area of microbiology, new shipments of test kits or strips used for organism identification should be tested with organisms giving positive and negative reactions for each test before or concurrent with initial testing of clinical isolates. This includes identification kits or panels that are inoculated and read manually, and those that are part of an automated instrument system. We are retaining the requirement formerly at § 493.1218(f)(1) (now at § 493.1256(e)(1)) that laboratories check each batch (prepared in-house), lot number (commercially prepared), shipment of reagents, disks, stains, antisera, and identification systems (systems using two or more substrates and/or reagents) when prepared or opened for positive and negative reactivity. We do not believe additional testing of these systems is needed if they are stored and maintained under appropriate conditions. Further testing is only necessary if labile reagents must be prepared or used each time the kit is used or if specified by the manufacturer.

Comment: Several commenters requested clarification of the control requirement at § 493.1218(b)(1) for qualitative tests as applied to microbiology procedures. The commenters asked which of the biochemical tests or media used for microbial identification would be considered qualitative tests.

Response: Biochemical tests using specific reagents or growth tests that employ selective or differential media (for example, indole tests, citrate media) that are a part of the total system of identification from culture are not considered qualitative tests in microbiology. Therefore, we are retaining the requirement formerly at § 493.1218(f)(1) (now at § 493.1256(e)(1)) that states laboratories must check each new batch (prepared in-house), lot number (commercially prepared), and shipment when prepared or opened for positive, negative, and graded reactivity, if applicable. Specifically, former § 493.1218(f)(4) (now at § 493.1256(e)(1) and (4)) requires each batch of media to be checked before or concurrent with initial use for sterility, and its ability to support, select, or inhibit growth, as intended, and/or provide the appropriate biochemical response. The manufacturer's control checks of media may be used if the product insert specifies they meet the NCCLS standards for media control testing. These individual procedures do not require control checks with each run of patient specimens or further testing unless specified by the manufacturer or under specialty or subspecialty control requirements. Biochemical tests or media that provide microbial identification from a direct specimen or culture (for example, direct antigen tests for group A streptococcus, bacterial serotyping from culture) are considered qualitative microbiology tests and are graded for reactivity. We are retaining the control procedures requirements for qualitative test systems formerly at § 493.1218(b)(1) (now at § 493.1256(d)(3)(ii)).

Comment: One commenter recommended we add ''XV discs or strips'' to § 493.1227(a)(2) that requires testing both positive and negative control organisms each week of use, and delete § 493.1227(b) that requires testing the XV discs or strips with only a positive control organism each week of use.

Response: Testing of XV discs or strips was limited to only a positive control each week of use because there is no known available control to check negative reactivity for the group of organisms that this test identifies. We are deleting the specific QC requirements for testing X, V, and XV disks or strips. These disks or strips are now subject to the general control procedure requirements formerly at § 493.1218(f)(1) (now at § 493.1256(e)(1)) that include testing each new batch (prepared in-house), lot number (commercially prepared), and shipment when prepared or opened for positive and negative reactivity. Since there is no control available to check negative reactivity for XV disks or strips, the use of only a positive control for XV disks or strips will be deemed to meet the CLIA regulation as specified in Appendix C of the State Operations Manual (CMS Pub. 7).

Comment: Several commenters recommended we change the control requirement for daily testing of antimicrobial susceptibility procedures to a weekly requirement, as specified by NCCLS. One commenter also suggested manufacturers develop control procedures consistent with NCCLS antimicrobial susceptibility testing standards whenever feasible.

Response: CLIA requires daily control checks for antimicrobial susceptibility testing, formerly at § 493.1227(c)(2) (now at § 493.1261(b)(1)) unless CMS approves a procedure that provides equivalent quality testing as specified in Appendix C of the State Operations Manual (CMS Pub. 7). In this case, the procedure providing equivalent quality testing is the NCCLS standard allowing the laboratory to perform weekly control testing of antimicrobial susceptibility procedures after establishing accuracy control limits through initial daily testing. The laboratory may continue performing weekly control testing provided the control results do not exceed the established limits.

Comment: One commenter requested clarification of the control requirements for antimicrobial susceptibility testing

with regard to the frequency of testing the disks, media, and overall procedure. The commenter felt that there is a contradiction between §§ 493.1227(c) and (c)(2) and that one of these statements should be deleted.

Response: In the former regulation, antimicrobial susceptibility testing requires that whenever a new batch of media or a new lot number and shipment of antimicrobial agents (disks) are put into use, the laboratory must verify that the media and agents perform within acceptable control parameters for testing. Following this initial verification that the test components (that is, media and antimicrobial agents) are working appropriately, the test procedure must be checked routinely with appropriate control strains to ensure that it is being performed accurately and all components of the procedure continue to work properly. This routine control procedure must be performed each day of patient testing or can be performed weekly. The weekly QC testing will be deemed to meet CLIA requirements, if performed as specified in the approved procedure providing equivalent quality testing in Appendix C of the State Operations Manual (CMS Pub. 7). The control organisms must be within established control limits before patient results can be reported.

Although we did not intend for the requirements at §§ 493.1227(c) and (c)(2) to appear contradictory, we are revising the language now at § 493.1261(b) for clarification of these requirements. In addition, we are making conforming changes to the language pertaining to the requirements for antimycobacterial and antifungal susceptibility testing for consistency and to be current with testing performed in these subspecialties. These requirements, formerly at §§ 493.1229(d) and 493.1231(d), are now at §§ 493.1262(b) and 493.1263(b).

Comment: A number of commenters stated the control requirements for identification procedures used in mycobacteriology at § 493.1229(a) should not selectively require positive and negative acid-fast control organisms to check the iron-uptake test each day of use while requiring only a positive acid-fast control for all other procedures. The commenters recommended that all identification procedures used in mycobacteriology be tested each day of use with an acid-fast organism that produces a positive result, and an acid-fast organism that produces a negative result.

Response: We agree with these commenters and because the incidence of infection caused by a variety of mycobacteria is increasing significantly, it is important for laboratories to accurately identify individual species within this genus. This results in increasing numbers and types of identification procedures being performed and it is critical that the accuracy of each of these tests be verified each day of use. This can best be ensured each day of use by including both an acid-fast control organism that produces a positive reaction and an acid-fast control organism that produces a negative reaction for each test. We are revising the requirement formerly at § 493.1229(a) (now at § 493.1262(a)) to reflect this change.

Comment: One commenter expressed concerns regarding the expense of testing controls and stated that the frequency for checking positive and negative reactivity of the BACTEC NAP test used to identify *M. tuberculosis* should be changed from each day of use to each week of use. This commenter suggested the requirement for testing a positive control each day of use could be satisfied by subculturing the growth from the BACTEC bottle to a solid media to detect appropriate colony and microscopic morphology.

Response: The control requirements were written to address test complexity and specialties or subspecialties of testing, not specific test systems or procedures. Test-specific CLIA regulations are only developed when tests are not adequately addressed in the general or specialty or subspecialty requirements. The commenter requested a change in CLIA regulation because of the expense of performing controls each time the BACTEC NAP test is set up. The alternative method that the commenter suggests for a positive control is not actually a control on the ability of the NAP test to inhibit growth of *M. tuberculosis,* but is a confirmatory test for the presence of this organism.

Although we agree with confirming results of the NAP test, it is not the same as using positive and negative control organisms to check the NAP vials for their ability to inhibit growth of *M. tuberculosis* and to allow growth of other mycobacteria. However, we understand the financial concerns associated with running positive and negative controls each day of use for this test. Since the test has a growth control included as part of each test, and the manufacturer indicates the media is stable and does not recommend testing positive and negative organisms as frequently as each day of use, we agree with the commenter that laboratories should only be required to check positive and negative control organisms each week of use. In addition, we are specifying this requirement as provided at § 493.1256 as an alternative procedure in Appendix C of the State Operations Manual (CMS Pub. 7).

Comment: One commenter stated positive and negative reactivity should be checked each day of use for all acid-fast staining procedures, rather than each week of use.

Response: We agree with the commenter that both fluorochrome and conventional acid-fast stains should be tested more frequently than each week of use and that both positive and negative control organisms should be tested. Nonpathogenic mycobacteria in water supplies have been found to contaminate buffers, rinse water, or other reagents, producing false positive staining results. Given the widespread use of acid-fast stains with the increasing incidence of mycobacterial disease, it is critical that the accuracy of these tests be verified each day of use. Therefore, we are deleting the requirements formerly at §§ 493.1229(b) through 493.1229(c) for testing fluorochrome and conventional acid-fast stains each week of use. The requirement for testing conventional acid-fast stains will now default to the general control requirement for stains formerly at § 493.1218(f)(2) (now at § 493.1256(e)(2)) that requires testing staining materials for intended reactivity each day of use. For stains that provide positive and negative reactivity (intended reactivity), we are revising the language to clarify that stains must be tested with positive and negative controls each day of use. By eliminating the subspecialty requirement for fluorochrome acid-fast stains, the general control requirement for fluorescent stains formerly at § 493.1218(f)(3) (now at § 493.1256(e)(3)) becomes applicable to these procedures. This general requirement specifies testing for positive and negative reactivity each time of use. It is appropriate to require the same control testing for fluorochrome acid-fast stains as are required for all other fluorescent stains.

Comment: One commenter recommended the deletion in bacteriology of testing positive and negative organisms each week of use for acid-fast stains as required in § 493.1227(a)(2) and replacement of the mycology term ''acid-fast stain'' at § 493.1231(c), with ''modified acid-fast stain.'' This commenter emphasized that acid-fast stains are used in mycobacteriology rather than bacteriology, and that the procedure for staining used in mycology is a modification of the acid-fast stains performed in mycobacteriology.

Response: We agree with this commenter on both of these points. Although acid-fast stains are occasionally performed in bacteriology, by deleting the requirement in bacteriology for testing acid-fast stains each week of use, it defaults to the general requirement formerly at § 493.1218(f)(2) (now at § 493.1256(e)(2)) that requires laboratories to test staining materials for their intended reactivity (including positive and negative reactivity, as appropriate) each day of use. We agree with the commenter that the staining procedure in mycology is a modification of acid-fast stain used in mycobacteriology; therefore, we are deleting the requirement formerly at § 493.1231(c) for performing control testing each week of use for (modified) acid-fast stains. Again, this results in the control requirement for these stains defaulting to the general requirement for testing each day of use and is reasonable based on the fact that we are now requiring positive and negative controls for all acid-fast stains each day of use.

Comment: One commenter stated that the control regulation for mycology and mycobacteriology should require the use of a safety cabinet when testing in these specialty areas.

Response: We agree with the commenter that safety is an important factor in laboratory testing, formerly at § 493.1204(b) (now at § 493.1101(d)) and laboratories are required to maintain a safe testing environment. Safety precautions must be established and observed to ensure protection from biohazardous materials. Under §§ 493.1445(e)(2) and 493.1407(e)(2), the laboratory director is responsible for ensuring a safe environment is provided for employees conducting non-waived testing. In addition, other government agencies enforce State and local laws and other Federal standards that ensure protection of employees and the public from biohazardous materials. These agencies include the Occupational Safety and Health Administration and the Environmental Protection Agency.

Comment: One commenter stated that the wording at § 493.1235(c) is inappropriate. The commenter recommended the replacement of the word ''culture'' (referring to uninoculated controls) with ''incubate'' or ''hold.'' This individual stated that the use of the term culture as specified at § 493.1235(c) generally means to inoculate and inspect for growth.

Response: We agree with this commenter and are replacing the term ''culture'' with the term ''incubate'' formerly at § 493.1235(c) (now at § 493.1265).

Comment: A commenter requested clarification of the control requirements for virology as they pertain to direct antigen detection. This commenter recommended the addition of a statement to § 493.1235 following paragraph (c) that would read ''The above QC requirements are not applicable to virology testing performed using direct antigen detection methods.''

Response: We agree with the commenter that the wording formerly at § 493.1235(c) needs clarification. There are several types of tests that identify viruses, but this requirement only applies to cell culture methodologies used to isolate and identify viruses. Therefore, we are changing the language for this requirement, now at § 493.1265(a), to make it specific to cell culture methodologies.

Sections 493.1237 Condition: Diagnostic Immunology; 493.1239 Condition: Syphilis Serology; and 493.1241 Condition: General Immunology

Specific comments received and response to comments regarding §§ 493.1237, 493.1239, and 493.1241 are set forth below.

Comment: A commenter stated § 493.1239(e) and § 493.1241(d), which refer to facilities manufacturing blood and blood products, should be deleted. This individual believes CLIA regulations should not cover manufacturing requirements.

Response: We disagree with the commenter. These requirements refer to testing requirements under CLIA regulations (donor specimens) regardless of where the testing is performed. However, we are moving these requirements, formerly under the subspecialties of syphilis serology and general immunology, and placing them with other requirements addressing the immunohematological collection, processing, dating, labeling, testing, and distribution of blood and blood products now at § 493.1271, Immunohematology (formerly at § 493.1273(a)).

Comment: One commenter requested clarification of the QC requirements for serological testing (both syphilis serology and general immunology) to run patient specimens concurrently with a positive serum control of known titer or controls of graded reactivity, if applicable, and a negative control. Specifically, this commenter questioned if these requirements refer to the additional controls run on a new kit to verify reproducibility, or if they pertain to the daily testing of the positive controls supplied in commercial kits. Other commenters objected to including two control materials each time patient testing is performed. One commenter thought only a positive control was necessary for immunology tests if the patient results were negative.

Response: We agree with the commenters who objected to the syphilis serology and routine immunology requirements requiring two control materials each time patient testing is performed. With the development of more accurate and stable test systems, the requirements formerly at § 493.1239(b) and § 493.1241(a) for assaying controls concurrently with patient specimens are excessive for many of the test systems. We are, therefore, deleting these requirements. Laboratories performing these tests will now need to meet the applicable control procedures at § 493.1256. In addition, the laboratory must meet the requirements that pertain to establishing or verifying a test system's performance specifications before putting a new test system into routine use formerly at § 493.1213 (now at § 493.1253).

We disagree with the comment that testing only a positive control is sufficient if the patient results are negative. Laboratories, at a minimum, must follow the manufacturer's instructions and for qualitative tests, assay a positive and negative control each day of patient testing (now at § 493.1256(d)(3)(ii)). For procedures producing graded or titered results, a control material with graded or titered reactivity, as applicable, and a negative control material must be assayed each day testing is performed formerly at §§ 493.1239(b) and 493.1241(a) (now at § 493.1256(d)(3)(iii)). The control material supplied in commercial kits (test systems) may be used to meet the requirements formerly at §§ 493.1239(b) and 493.1241(a) (now at § 493.1256(d)(3)(iii)) providing the material is of known reactivity (titered or graded, as applicable) and is not the same material used to establish a cutoff or calibrate the test system if calibration of the test system is required (now at 493.1256(d)(9)).

Section 493.1245 Condition: Routine Chemistry

Specific comments received and response to comments regarding § 493.1245 are set forth below.

Comment: One commenter expressed concern that §§ 493.1245(c) and (d) could be interpreted to mean that the same material could be used to calibrate the instrument and verify or control the test run for blood gas analyzers. The commenter stated that this would not

detect problems arising from deteriorated or contaminated calibrating solutions. The commenter also recommended the reference to calibrators be deleted from these sections and that control testing be performed using only control material.

Response: We agree with this commenter. It was never our intent to infer by the wording of these requirements that calibration material used to calibrate a test system could be used as a control to monitor the test system's performance. However, we allow the use of calibration material as a control material provided it is from a different lot number than that used to calibrate the test system or establish a cut-off. Therefore, we are clarifying the use of calibration materials as control materials (now at § 493.1256(d)(9)), and eliminating the terms ''calibration'' and ''calibration material'' from the blood gas analysis requirements (now at § 493.1267).

Comment: One commenter stated testing one sample of blood gas control per 8 hours of patient testing is not sufficient and is inconsistent with the general requirement for quantitative tests at § 493.1218(b)(2) that requires two controls of different concentrations with each run of patient specimens. This commenter recommended that at least two levels of control be required every 8 hour shift.

Response: We revised the general control requirement formerly at § 493.1218(b) (now at § 493.1256(d)). The requirement now specifies, at a minimum, assaying two levels of control materials each day patient specimens are tested. We are deleting the term ''run'' from the regulation. Also, laboratories must perform control testing using the number and frequency specified by the manufacturer or established by the laboratory when those frequencies meet or exceed the minimum requirement. Therefore, the minimum control requirement for quantitative tests, unless a more frequent interval is recommended by the test system's manufacturer or the laboratory, is two control materials of different concentrations each day patient specimens are tested.

The requirement for one control material per 8 hours for blood gas analyses, formerly at § 493.1245 (now at § 493.1267) exceeds these general QC requirements. The blood gas control requirements also require the laboratory to use a combination of control materials that check low and high values each day of testing. In addition, for blood gas instruments that do not internally verify calibration at least every 30 minutes, the laboratory must include one sample of control material each time patient samples are tested. This final rule provides minimum requirements. Based on the laboratory's verification of the test system's performance specifications before routine patient use (now at § 493.1253) and establishment of its control procedures (now at § 493.1256(d)), the laboratory may determine that it needs to run additional control materials or run control materials at a more frequent interval to assure accurate and reliable test results.

Section 493.1249 Condition: Toxicology

Specific comments received and response to comments regarding § 493.1249 are set forth below.

Comment: One commenter asked that the term ''drug abuse screening using thin layer chromatography'' at § 493.1249, Toxicology be modified to read ''drugs-of-abuse screening using thin layer chromatography'' (''drugs-of-abuse'' is defined by the National Institute for Drugs of Abuse now National Substance Abuse and Mental Services Health Administration Laboratory Certification Program). This commenter also requested deletion of the requirement under § 493.1249(b) for at least one control sample to be processed and included in each chamber, stating that all environmental, chemical and material variables within a chamber are visualized by running calibration materials. The commenter added that controls should be analyzed with each run, and that each run should not exceed a 24 hour period.

Response: We agree with the commenter that the control requirements formerly at § 493.1249 are not clear; therefore, we are revising the language to clarify the requirements. We are moving the requirements for thin layer chromatography to § 493.1256(d)(4) under Control procedures. In addition, we are revising the term ''drug abuse screening'' to read ''all known substances or drug groups'' identified and reported by the laboratory, to accommodate the wider use of the technology. However, we disagree with the commenter's statement that analyzing one control material per 24 hours is sufficient. If extractions and tests are performed more frequently than once per 24 hours, each ''plate'' or ''card'' (formerly referred to as ''chamber'') must be spotted with at least one sample of control material to ensure that appropriate separation, and as applicable, extraction took place. The inclusion of a calibration material containing all known substances or drug groups reported by the laboratory using thin layer chromatography on each plate or card ensures appropriate identification of the substances or drugs in patient specimens.

Section 493.1253 Condition: Hematology

Specific comments received and response to comments regarding § 493.1253 are set forth below.

Comment: We received several comments requesting the deletion of QC requirements in hematology because they would increase laboratory costs.

Response: We agree with the commenters that the requirement to include two levels of control material each 8 hours of testing for automated hematology analyzers (for example, cell counters and differential counters) is somewhat excessive in light of the proven stability and reliability of these instruments. Therefore, we are deleting the specialty-specific control requirement for automated hematology analyzers formerly at § 493.1253(b), and are requiring laboratories to meet the general control requirements (now at § 493.1256(d)) when using automated hematology analyzers. However, the manufacturer's instructions and the laboratory's evaluation of the instruments' stability, environmental effects, and operator variance will determine the actual number, type, and frequency of testing control materials. At a minimum, the laboratories will have to test two control materials of different concentrations each day.

Comment: One commenter requested that we remove the requirement for duplicative testing of patient and control specimens for manual coagulation tests, as required at § 493.1253(d)(2), since proficiency testing requirements do not allow for duplicative testing.

Response: We disagree with the commenter and are retaining the requirement for duplicative testing of patient specimens and control materials for manual coagulation testing (now at § 493.1269(c)(2)). CLIA regulations for proficiency testing (PT) (§ 493.801(b)(2)) require the laboratory to test PT samples the same number of times that it routinely tests patients' samples. Therefore, since patient specimens must be routinely tested in duplicate, PT samples for manual coagulation testing must also be tested in duplicate.

Section 493.1257 Condition: Cytology and Section 493.1259 Condition: Histopathology

Approximately 66 percent of the 1,030 comments received concerning the final rule with comment period,

subpart K, were in response to the cytology requirements. The comments were primarily from professional organizations, cytotechnologists, pathologists, and other physicians. The major issues that commenters addressed include—

(1) Workload limits; (2) review of reactive reparative cases by a technical supervisor; (3) the 10 percent rescreen of negative cases screened by a cytotechnologist; and (4) the 5-year retrospective review of negative smears from patients with a current high grade lesion.

Specific comments and response to comments regarding §§ 493.1257 and 493.1259 are set forth below.

Comment: Several commenters stated the language ''non automated microscopic technique'' used to describe the slides that are counted in the workload limit is inappropriate and might be confused with slides that are screened using a motorized mechanical stage or with slides that are read by an automated instrument.

Response: We agree with the commenters and are removing the wording ''non automated microscopic technique.'' We also want to emphasize that slides that are read with a human component must be included in the 100 slide limit; slides that are read by an automated instrument that do not require human review are not included in the workload limit.

Comment: A number of commenters and one cytology organization were opposed to establishing the workload limit at 100 slides examined in a 24 hour period. A few commenters felt the workload limit was too restrictive, while other commenters and the cytology organization indicated the limit was too high.

Response: The CLIA statute at section 353(f)(4)(B)(i) specifically states that the standards must establish ''the maximum number of cytology slides that any individual may screen in a 24 hour period.'' Limiting the number of slides that may be examined in 24 hours to no more than 100 is the absolute maximum workload limit for an individual. However, we agree with the commenters that this may not be an appropriate workload for all individuals. To clarify our position, formerly at § 493.1257(b)(1) (now at § 493.1274(d)(2)), we specify that the Federal workload limit was not to be used as a performance target for cytology personnel. In addition, we specified formerly at § 493.1257(c)(4) (now at § 493.1274(d)(1)) that the cytology technical supervisor must establish a workload limit (not to exceed 100 slides examined per 24 hours) for each person examining slides and that at least every 6 months, the technical supervisor must re-evaluate and adjust, if necessary, each individual's workload limit. In addition, we are emphasizing that the workload limit applies only to individuals and does not apply to automated slide examination systems that may be used to screen slides and identify those smears requiring no human microscopic examination.

Comment: One organization asked whether the workload requirements are applicable to technical supervisors or only to cytotechnologists. Several commenters suggested the workload requirement only applies to cytotechnologists.

Response: The workload requirements apply to any individual who performs primary screening of cytology slides. This may be a technical supervisor or a cytotechnologist. We are also clarifying that while tissue pathology slides and previously examined gynecologic and nongynecologic slides are not included in the 100-slide workload limit for technical supervisors, the technical supervisor must subtract the time spent evaluating these slides and the time spent on any nonscreening duties from the time spent screening slides to appropriately adjust the workload.

Comment: Many commenters and the cytology professional organizations opposed the workload provision to count as one-half slide those smears made using automated, semiautomated, or other liquid-based slide preparatory techniques that result in cell dispersion over one-half or less of the slide. Some commenters indicated that this workload limit should apply only to nongynecologic preparations, while others thought it premature to use this calculation for any cytologic preparations until sufficient scientific studies have been completed to document the establishment of a workload limit appropriate for these preparatory techniques.

Response: In order to address concerns of the commenters, we are making several clarifications. First, the 200-slide workload limit was initially established in the February 28, 1992 final rule with comment period published in the **Federal Register** (57 FR 7002) in response to innovations in cytology preparatory techniques and acknowledgment that slide preparations that only occupy a portion of the slide will not count as a whole slide. Slide preparations (gynecologic and nongynecologic) made using automated, semi-automated, or other liquid-based preparatory techniques that result in a specimen that only occupies a small portion of the slide, are counted as one-half slide. Second, on January 19, 1993, we published a final rule with comment period in the **Federal Register** (57 FR 5212) removing gynecologic preparations. On July 22, 1993, we published a technical correction notice in the **Federal Register** (58 FR 39154) that inadvertently reinserted gynecologic preparations. In addition, Cytyc, manufacturer of ThinPrep ™, agrees that a 200-slide workload limit is too high for gynecologic preparations and has requested that the 200 slide workload limit not be applicable to gynecologic slides. We agree with the commenters and Cytyc corporation, and we are eliminating gynecologic slides from the 200-slide workload limit (now at § 493.1274(d)(2)(iii)). The 200-slide workload limit will only apply to nongynecologic slides.

Comment: Many Commenters and the Cytology organizations agreed that a workload limit was appropriate for gynecologic preparations. However, they were opposed to establishing a workload limit for nongynecologic smears because these preparations vary greatly in specimen type or source, preparatory techniques, and cellularity requiring various time frames for evaluation. The commenters acknowledged the difficulty in establishing a workload limit for individuals who examine nongynecologic preparations exclusively or a combination of gynecologic and nongynecologic smears. For fine needle aspirations, several organizations suggested using the methodology employed by New York State to prorate nongynecologic preparations, that is, for cases involving one to three slides, each slide is counted as one and for cases having four or more slides, a maximum of three slides are counted for workload purposes.

Response: We agree with the commenters that it is easier to establish a workload limit for gynecologic smears than for nongynecologic preparations because of the variability in nongynecologic preparations; however, the statute requires us to determine the maximum number of cytology slides that an individual can screen in a 24-hour period. Therefore, the workload limit is applicable to all cytology slides, including gynecologic and nongynecologic preparations. Concerning the New York State proration of nongynecologic slides, this practice is no longer in use in New York.

Comment: Several individuals asked for clarification on the specific guidelines that a technical supervisor should use to determine the maximum workload for an individual. Some

commenters noted the technical supervisor may have to justify a workload that is lower than 100 slides to hospital and laboratory administrators.

Response: Formerly at § 493.1257(c)(4)(i), individual workload is based on the performance evaluation described formerly at § 493.1257(c)(3). Therefore, we are revising the requirement, now at § 493.1274(d)(1)(i), to make it more understandable. Performance must be evaluated using the following: (1) Re-evaluation of 10 percent of the cases interpreted to be negative by cytotechnologists; and (2) comparing the cytotechnologist's interpretation with the final diagnosis on cases of atypical squamous cells of undetermined significance (ASC–US), low-grade squamous intraepithelial lesion(LSIL), high-grade squamous intraepithelial lesion (HSIL), glandular epithelial cell abnormalities, or other malignant neoplasms. However, the evaluations listed in the former CLIA regulations must be viewed as minimal requirements and the laboratory may have additional mechanisms or criteria to evaluate individual performance. For example, the following provisions in the CLIA regulations may be used: (1) Number of discrepant findings on the retrospective review of previous negative cases from patients with a current HSIL, adenocarcinoma or other malignant neoplasm; (2) individual statistics evaluated against the laboratory's overall statistics; and (3) competency assessment activities.

Comment: Many of the commenters and the cytology organizations suggested that the requirement for confirmation of cases by the technical supervisor be limited to those having atypical squamous or glandular cells, or any premaligment or malignant cell changes. The commenters suggested deleting the reference requiring confirmation of ''reactive or reparative changes,'' stating that the requirement was excessive. Other commenters recommended changes to allow technical supervisors the discretion to determine the level of supervisions, that is, review of cases with benign cellular changes, needed by each employee. In addition, several commenters suggested we revise the language to include the Bethesda terminology.

Response: We have not removed all reference to reactive and reparative changes because many laboratories still use this classification. The regulation, however, incorporates the Bethesda terminology, which provides for a uniform categorization of the cellular changes seen in gynecologic cytology. Most of the slides formerly classified as having ''reactive and reparative'' changes that would have exhibited marked or extensive cellular changes on technical review will, therefore, be classified as ASC–US or as having a squamous cell abnormality under the Bethesda terminology. As specified at § 493.1274(e), all of these slides are required to be reviewed by the technical supervisor. However, we have retained the classification reactive and ''reparative changes,'' and similar cellular changes under the Bethesda category ''Negative for Intraepithelial Lesion or Malignancy'' that would formerly have been categorized as reactive or reparative to encompass those slides needing review by the technical supervisor. Technical supervisors continue to have the discretion to review more cases as necessary to train and manage cytotechnologists under their supervision. Although we are not requiring the use of the Bethesda terminology, the majority of the laboratories have adopted it, and we encourage other to do the same.

Comment: One organization stated that the technical supervisor's signature on the worksheet is acceptable documentation for the review of abnormal gynecologic cases. For nongynecologic cases, the organization suggested that laboratories allow the technical personnel to verify the final computer generated report that would include the name of the technical supervisor who reviewed the case. Another commenter asked for clarification on electronic signatures and whether CLIA regulations allow electronic requisitions.

Response: We do not believe that any change in the CLIA regulations is appropriate. The final report must be verified by the technical supervisor who reviewed the case and signs the report, and electronic signatures must be authorized and verified by the technical supervisor who signs the report. As specified at § 493.1241, electronic requisitions are acceptable, as long as the requisition contains the required information.

Comment: Several commenters, including one cytology organization, disagreed with requiring laboratories to rescreen 10 percent of the cases interpreted to be normal or negative by cytotechnologists. One organization stated the 10 percent rescreen is a statistically invalid mechanism for reducing the false negative rate and suggested the requirement be replaced by a goal-oriented statistically valid system for promoting laboratory QC. One organization was opposed to requiring laboratories to complete the 10 percent rescreen before reporting patient results.

Response: The CLIA statute requires ''* * * random rescreening of cytology specimens determined to be in the benign category * * *'' Accordingly, random rescreening of negative cases is required in CLIA rules. We view the 10 percent rescreen as a minimum requirement and only one component of the laboratory's control procedures and QA activities. In addition, rescreening is supported by the results of cytology surveys conducted under CMS contract that includes rescreening approximately 0.1 percent of the laboratory's caseload. In many of these surveys, diagnostic discrepancies were noted between the contractor's evaluation of patient specimens and the results reported by the laboratory, even though the sample rescreened was less than 10 percent of the laboratory's caseload. The control procedures, including the 10 percent rescreen, assess the quality of the laboratory's results, and the rescreen must be completed before issuing patient reports on the slides selected for the 10 percent rescreen as specified formerly at § 493.1257(d)(1)(iii) (now at § 493.1274(c)(1)(ii)).

Comment: One commenter asked whether the 10 percent re-evaluation of negative cases could be performed by the same individual who performed the primary review.

Response: The 10 percent rescreen of negative cases is one provision of the cytology control procedures specified formerly at § 493.1257(d) requiring laboratories to have a program designed to detect errors in cytology examinations. This provision is now at § 493.1274(c). Ten percent of the cases interpreted as negative by cytotechnologists must be reevaluated by a cytology technical supervisor qualified under §§ 493.1449(b) or 493.1449(k), a cytology general supervisor qualified under § 493.1469(b)(2), or a cytotechnologist qualified under § 493.1483 who has the experience specified in § 493.1469(b)(2). For laboratories with a solo pathologist (no cytotechnologists), the 10 percent rescreen need not be performed; however, the following cytology QC procedures must be performed: a laboratory comparison of clinical information and histopathology reports (as specified at § 493.1274(c)(2)), a retrospective rescreen of normal and negative cases received within the previous 5 years from a patient with a current high grade lesion (as specified at § 493.1274(c)(3)) and annual statistical evaluation (as specified at § 493.1274(c)(5)).

Comment: Many cytology organizations disagreed with requiring review of all normal or negative slides from the previous 5 years for any patient having a current high grade intraepithelial lesion or above. The commenters felt that the 5-year review was unreasonable and unnecessarily burdensome and suggested that the review include only the two most recent smears, if available in the laboratory. A number of commenters noted the error at § 493.1257(d)(3) in referring to patients with ''a current high grade or above intraepithelial lesion . . .'' and suggested rewording the requirement for retrospective review of negative cases from patients having a ''current high grade intraepithelial lesion or cancer.''

Response: We are not reducing the requirement for review of negative cases from the previous 5 years for patients having a current high grade intraepithelial lesion or cancer because the law requires ''. . . for each abnormal cytological result, rescreening of *all* (emphasis added) prior cytological specimens for the patient, if available.'' However, we appreciate and agree with the commenters' suggestion about rewording the requirement, formerly at § 493.1257(d)(3) (now at § 493.1274(c)(3)) to reflect current terminology.

Comment: One organization asked for clarification on the time frame for completion of the retrospective review of cases with a current high grade lesion or above and the histology and cytology correlation.

Response: The retrospective review and the histology and cytology correlation are part of the control procedures and must be completed in a timely manner. Since there is a possibility that this QC activity could result in the issuance of a corrected report that may affect patient treatment, the laboratory must have procedures in place that include time frames for these activities.

Comment: Several commenters and cytology organizations disagreed with requiring laboratories to compare the case reviews of each individual with the laboratory's overall statistical values. The commenters stated that the case mix (specimens from various clinics with different patient populations) varies and these statistics should not be used to assess individual performance. In smaller laboratories the statistical comparison may not be valid due to the small numbers. It was suggested that laboratories be given flexibility to determine the best approach for implementing the control procedure requirements and evaluating individual performance.

Response: We established these requirements as a result of comments provided in response to the proposed rule that was published on May 21, 1990 in the **Federal Register** (55 FR 20896). The commenters stated that reviewing the laboratory's data provided useful information on overall laboratory practice as well as individual performance. We believe these requirements have provided valuable information for assessment of laboratory and individual performance; therefore, we are not making any revisions. However, laboratories may document situations that affect the laboratory's statistics and individual case reviews.

Comment: One cytology organization was opposed to requiring laboratories to document cases for which histologic reports were unavailable for comparison with abnormal gynecologic results, stating that it was time consuming and burdensome and provided no benefit to the patient.

Response: In an attempt to minimize the burden, (now at § 493.1274(c)(5)(iv)), we are requiring documentation of only the number of cases that have histology correlation. We believe this information is necessary to determine the laboratory's success in obtaining histology reports for the histology and cytology correlation.

Section 493.1259 Condition: Histopathology

Specific comments received and response to comments regarding § 493.1259 are set forth below.

Comment: Two medical professional organizations disagreed with the requirements at § 493.1259(c) that precluded neurologists from examining nerve and muscle biopsies. Also, in May 1993, CLIAC recommended that neurologists with specialized training and board certification qualify as technical supervisors, general supervisors, and testing personnel of neuromuscular histology. Without recognition of this training, neurologists would be required to refer neuromuscular tissue specimens to an anatomic pathologists for examination.

Response: We are amending the histopathology QC requirements formerly at § 493.1259(c) (now at § 493.1273(c)) to allow individuals who have successfully completed a training program approved by HHS to examine and provide reports for neuromuscular pathology. In Appendix C of the State Operations Manual (CMS Pub. 7), subpart K, we will specify that the training program developed by the American Academy of Neurology Committee for Neuromuscular Pathology is approved by HHS. We are making the change to § 493.1273 rather than the personnel requirements in subpart M, because in this final rule, we are limiting the personnel revisions to the phase-in provisions addressed in the December 28, 2001 proposed rule. HHS received numerous personnel comments in response to the February 28, 1992 final rule with comment period which we intend to address in a future regulation.

Section 493.1265 Condition: Histocompatibility

Specific comments received and response to comments regarding § 493.1265 are set forth below.

Comment: Several commenters were pleased with the final CLIA rule for histocompatibility testing and felt the majority of the concerns raised over the proposed rule had been addressed. They noted the requirements now generally reflect the state of the art laboratory practices in this specialty area of testing that is continuing to evolve.

Response: We appreciate this acknowledgment of the efforts made in developing the histocompability QC requirements specified in the final rule with comment period that was published on February 28, 1992 in the **Federal Register** (57 FR 7170). In our continuing endeavor to represent current technology and practice, we are updating some of the terminology and references used in this section. We are also deleting several requirements that are duplicative of requirements found elsewhere in the CLIA regulation. In addition, we are adding clarifying language and reorganizing the requirements in this section that apply to HLA typing, disease associated studies, antibody screening, crossmatching, transplantation, and general requirements that apply to every histocompatibility laboratory regardless of the testing and services offered by the laboratory.

Comment: One commenter requested the requirements for histocompatibility testing be separated into three groups: solid organ transplantation, including renal; bone marrow transplantation; and histocompatibility testing for transfusion services.

Response: We acknowledge that the organization of the histocompatibility requirements found in the final rule with comment period may have caused some confusion to the reader trying to determine what testing requirements apply to each type of organ or tissue transplant. While there are various ways to group the requirements in this specialty, we are reorganizing this section by first delineating the general requirements for histocompatibility

testing (now at § 493.1278(a)) and specifying the requirements for HLA typing (now at § 493.1278(b)), disease associated studies (now at § 493.1278(c)), antibody screening (now at § 493.1278(d)), crossmatching (now at § 493.1278(e)) and transplantation (now at § 493.1278(f)). In addition, we believe this reorganization, along with other revisions, will greatly enhance the readability of this section and clarify the requirements that must be met for each type and level of histocompatibility testing performed by the laboratory.

Comment: One commenter pointed out the requirement at § 493.1265(a)(4) that addresses reagent typing sera inventories prepared in-house should also require that the specificity of the reagent be indicated. The commenter also requested clarification of the term ''typing tray'' used at § 493.1265(a)(9)(i) since the term can refer to any 96, 72, or 60 well microtiter tray used in the HLA laboratory. The commenter stated that without clarification, it is unclear whether the control requirements specified at this requirement refer only to trays used for HLA typing or if they include trays run in an attempt to identify the presence of circulating HLA antibodies.

Response: We agree that reagent specificity must be indicated on the laboratory's in-house prepared reagent typing sera inventory and are amending the requirement now at § 493.1278(a)(3) accordingly.

The commenter is correct to question the scope of the requirement formerly at § 493.1265(a)(9)(i) that addressed control requirements for typing trays. In addition, the term ''typing tray'' is somewhat restrictive in that testing performed with newer and emerging technologies may not necessarily use microtiter trays. Therefore, we are revising the requirement for clarification, and, with the reorganization of this section, § 493.1278(b)(6) now describes the controls a laboratory must use for each HLA typing, and § 493.1278(d)(6) addresses the controls a laboratory must use when performing antibody screening.

Comment: One commenter requested that the CLIA regulations mandate HLA antibody identification when panel screening studies indicate the presence of a lymphocyte-reactive antibody. In addition, the laboratory should determine if this is an autoantibody or alloantibody. The commenter also requested the CLIA rule require that the specific technique used in HLA antibody screening be at least as sensitive as the complement-dependent lymphocytotoxicity technique used in the final donor crossmatch.

Response: Histocompatibility testing is a rapidly evolving, highly complex specialty. Its role in predicting long-term allograft survival is the subject of numerous research studies. Not all antibody reactions have a defined specificity, and the clinical relevancy of each antibody has not been established. Mandatory antibody identification may be impractical, if not impossible, and uninformative in these cases. However, we agree that antibody identification must be performed when appropriate to support clinical transplant protocols and § 493.1445(e)(3)(i) requires the laboratory director to select test methods that are capable of providing the quality of results required for patient care. It is the laboratory director's responsibility to institute more stringent testing protocols as necessary for quality patient care. Therefore, we are adding a requirement at § 493.1278(d)(7) for laboratories that perform antibody identification to have available and follow written criteria and procedures for antibody identification to the level appropriate to support clinical transplant protocol.

We agree with the commenter that the laboratory must use a technique that detects HLA-specific antibody with a specificity equivalent or superior to that of the basic complement-dependent microlymphocytotoxicity assay. In addition, to detect antibodies to HLA Class II antigens, the laboratory must use a method that distinguishes antibodies to HLA Class II antigens from antibodies to Class I antigens. We are adding these two new requirements at §§ 493.1278(d)(1) and 493.1278(d)(2).

To ensure quality laboratory practices and for consistency with the two new requirements, we are specifying that techniques used for crossmatching must be documented to have increased sensitivity in comparison with the basic complement-dependent microlymphocytotoxicity assay (now at § 493.1278(e)(1)). In addition, when performing HLA typing, the laboratory must use a technique that is established to optimally define, as applicable, HLA Class I and II specificities (now at § 493.1278(b)(1)).

Comment: A number of commenters were opposed to the elimination of mandatory monthly screening for HLA antibodies, since most, if not all, laboratories lack access to accurate information regarding each potential transplant recipient's exposure to sensitizing events. This is compounded by the probability that not all potentially sensitizing events have been identified. A few commenters acknowledged that the cost of monthly screening can be prohibitive and suggested there may be some instances when monthly screening may not be necessary. However, most commenters agreed that studies need to be done to determine the optimum frequency of antibody screening.

Response: We agree with the commenters and recognize the importance of developing an accurate immunological history of the potential transplant recipient and the difficulty of identifying and obtaining information on all potential sensitizing events. We also appreciate the efforts to control healthcare costs by eliminating unnecessary and or redundant testing. To provide flexibility and allow responsiveness to emerging research data and information, we are revising the requirements formerly at §§ 493.1265(a)(2)(ii) and (a)(8)(i) (now at §§ 493.1278(d)(4) and (d)(5)) to require the laboratory to make a reasonable attempt to have available monthly serum specimens for all potential transplant recipients for periodic antibody screening and crossmatch. In this regard, the laboratory must have available and follow a policy, consistent with clinical transplant protocols for the frequency of screening potential transplant recipient sera for preformed HLA-specific antibodies.

Comment: Three commenters noted that DNA typing involves the genes rather than the expressed antigens; therefore, § 493.1265(a)(10) would be more accurate if changed to read, ''Compatibility testing for HLA class II polymorphisms should utilize techniques, for example, mixed lymphocyte culture, homozygous typing cells, or DNA analysis.''

Response: We agree with the commenters that the wording of the requirement formerly at § 493.1265(a)(10) is somewhat inaccurate and also believe that the requirement may be too restrictive for future methodologies, technologies, and transplantation protocols. Therefore, we are deleting this requirement for the laboratory to use specific techniques, for example, mixed lymphocyte cultures, to determine HLA Class II incompatibilities.

Comment: One commenter stated that the requirement at § 493.1265(a)(13) to have histocompatibility testing personnel evaluate unknowns on a monthly basis is excessive and should be reduced to once every 6 months.

Response: Histocompatibility testing is a highly complex specialty with great potential for harm to the patient if the testing is incorrectly performed. CLIA regulations specify formerly at

§ 493.1445(e)(13) that the director has to ensure that policies and procedures are established for monitoring employee competency and to identify needs for remedial training or continuing education. Monitoring employee competency may include the evaluation of previously tested specimens as unknowns. However, we are deleting this former requirement at § 493.1265(a)(13) because we believe it is somewhat duplicative of the laboratory director responsibility.

Comment: Three commenters, including a professional organization, recommended that living transplants be deleted from § 493.1265(b)(2) that requires the performance of mixed lymphocyte cultures or other augmented testing to evaluate HLA class II compatibility. The commenters stated that although appropriate for bone marrow transplantation, mixed lymphocyte culture is performed rarely in living-related kidney transplantation where HLA Class II compatibility and genetic linkages can be adequately determined using serological methods. In addition, the commenters maintained that mixed lymphocyte culture tests were unnecessary in solid organ transplants and not considered a contraindication to this type of transplantation.

Response: We agree with the commenters. The phrase, ''and living transplants,'' formerly at § 493.1265(b)(2), was deleted in a technical correction notice published on January 19, 1993. In addition, we recognize the evolving nature of transplant medicine makes it difficult to prescribe standards for testing protocols that may be quickly outdated with emerging research data and information, for example, graft survival, acute, and chronic rejection. For this reason we are revising the requirements formerly at §§ 493.1265(b) and (c) that specified the type of testing to be performed for each transplant type. We are requiring (now at § 493.1278(f)(1)) that laboratories performing histocompatibility testing for transfusion and transplantation purposes have available, and follow, written policies and protocols specifying the histocompatibility testing to be performed for each type of cell, tissue, or organ to be transfused or transplanted. The laboratory's policies must address, as applicable, testing protocols for cadaver donor, living, living-related and combined organ and tissue transplants; the level of testing required to support clinical transplant protocols (for example, HLA typing at the antigen or allele level); and any additional testing required for patients at high risk for allograft rejection. In addition, we believe this less prescriptive, but laboratory-specific requirement provides the flexibility required to ensure laboratory practice that is responsive to advances in transplantation medicine and laboratory methodologies and technology.

Comment: One commenter stated that the requirement, at § 493.1265(b)(3), to provide the results of the final crossmatch before nonrenal solid organ transplantation when the recipient has demonstrated presensitization is not necessarily relevant or realistic for all types of grafts. The commenter cited the short viability time of certain organs (heart and lung) and unpublished data pertaining to the nonrelationship between high-titered positive donor T cell crossmatches and liver allograft survival.

Response: We agree with the commenter that the period of time that organs, for example, the liver, pancreas, and heart remain viable after removal from the donor is often not sufficient for the laboratory to complete the crossmatch. The regulation formerly at § 493.1265(b)(3) (now at § 493.1278(f)(3)) has been revised to require laboratories to develop and follow policies for testing and providing results of final crossmatches when the recipient has demonstrated presensitization by prior serum screening. In addition, the policy must address emergency transplant situations that would not allow time for the laboratory to perform prospective crossmatches. In addition, we would like to clarify that the intent of § 493.1278(f)(3) is not to preclude the use of crossmatch-positive nonrenal organs and tissues but to ensure, whenever possible, the availability of all pertinent test results on which the physician(s) may base their decision to proceed with the transplant.

Section 493.1267 Condition: Clinical Cytogenetics

Specific comments received and response to comments regarding § 493.1267 are set forth below.

Comment: One commenter suggested the cross-references to subpart K at § 493.1267 list only those portions that apply to cytogenetic testing so that, for example, the general requirement for testing positive and negative controls is not referenced. The commenter suggested at the very least, Appendix C (Survey Procedures and Interpretative Guidelines for Laboratories and Laboratory Services) of the State Operations Manual (CMS Pub. 7) should instruct CLIA surveyors to ignore this requirement when inspecting a cytogenetics laboratory.

Response: The task of delineating all applicable requirements of subpart K for each specialty or subspecialty of testing would require continuous revision and updating for new test systems and emerging technologies. For this reason, the requirement (now at § 493.1225) remains unchanged and continues to direct laboratories to comply with the requirements of subpart K that are applicable to the testing being performed. However, Appendix C of the State Operations Manual will give guidance to surveyors concerning the control requirements for clinical cytogenetics. As specified now at § 493.1256(e)(2), each day of use, the laboratory is required to test the positive and negative reactivity of staining materials to ensure predictable staining characteristics. Media must be checked for sterility and to ensure that it supports growth of the appropriate tissues as required now at § 493.1256(e)(4). As for materials to demonstrate chromosome abnormalities, for example, linkage, breakage, or translocation, Appendix C of the State Operations Manual (CMS Pub. 7) states that these materials are not routinely available; however, an alternative procedure for the immediate assessment and monitoring of all testing over time must be instituted by the laboratory as specified now at § 493.1256(h).

Comment: A few commenters stated laboratory testing of sex chromatin by Barr body analysis or by ''Y'' body analysis is not considered the standard of practice for the diagnosis of individuals with sex chromosome aneuploidy, citing the well documented frequency of mosaicism in individuals with sex chromosome aneuploidy that leads to false negatives. Therefore, they strongly recommend not employing this testing as a screening test and deleting it from the list of tests that are performed in cytogenetics laboratories.

Response: We agree with the commenters and are deleting the requirements pertaining to the performance of X and Y chromatin counts for sex determination that were formerly at § 493.1267(a). In this final rule at § 493.1276(c), we are now requiring full chromosome analysis for sex determination.

Comment: A few commenters questioned the requirement that chromosome resolution be sufficient to support the reported result. One commenter stated that this is a ''catch 22'' in that a low resolution study reported as normal in a patient with an abnormality only detectable at a higher level of resolution would be wrong, however, the low resolution analysis would be in support of the reported

normal diagnosis. The commenters suggested establishing a specific band level of resolution that would be dependent upon the type of study requested.

Response: We are revising the requirement formerly at § 493.1267(b) (now § 493.1276(b)(2)) for clarity. The requirement now states that the resolution used must be appropriate for the type of tissue or specimen, and that the type of study required is based on the clinical information provided to the laboratory.

Comment: One commenter suggested that substituting the words ''photographic karyotypes'' for ''photographs'' would correctly reflect what cytogeneticists read.

Response: We are adding new language to the CLIA regulation formerly at § 493.1267(c) (now at § 493.1276(a)) to specify karyotypes in addition to photographs.

Comment: A few commenters disagreed with the CLIA regulation requiring ''appropriate nomenclature'' and felt the CLIA regulation should require the use of the International System of Cytogenetic Nomenclature in reporting all cases because it is the only recognized system that exists and anything else would be homemade and impossible to interpret other than by that particular laboratory.

Response: We agree with the commenters and are replacing the words ''appropriate nomenclature'' formerly at § 493.1267(d) (now at § 493.1276(d)) with the words ''the International System of Cytogenetic Nomenclature.''

Comment: One commenter stated that failure rate is an aspect of cytogenetic testing and that it is not addressed by CLIA regulations. The commenter also stated that failure rate can provide valuable information about a laboratory's capabilities and be easily evaluated by an individual lacking specific expertise in cytogenetics. The commenter stated that accepted standards for study failure rates exist for the various types of tests done in cytogenetic laboratories.

Response: We agree that study and culture failure rates can be a useful tool in evaluating a cytogenetic laboratory's performance. However, the study must be evaluated carefully because many factors outside of the laboratory's control may influence the rates, for example, specimen transit time and conditions. In addition, what constitutes failure must be clearly defined. For this reason, we are not mandating failure rates but encourage laboratories to monitor these rates as part of a QA program.

Comment: One commenter recommended gestational alpha-fetoprotein (AFP) be recognized as an analyte. Gestational AFP testing should not be included under Immunology, where AFP is used as a tumor marker.

Response: Although the analyte alpha-fetoprotein may be used for genetic screening, the test does not entail chromosomal examination (that is, cytogenetics). Measurement of this analyte may be used for non-cytogenetic purposes. CLIA certifies laboratories in both the subspecialty of routine chemistry and general immunology for gestational and maternal AFP.

Section 493.1273 Standard: Immunohematological Collection, Processing, Dating Periods, Labeling and Distribution of Blood and Blood Products

Specific comments received and response to comments regarding § 493.1273 are set forth below.

Comment: One commenter requested the addition of requirements to § 493.1273 regarding the use of bar code systems for the identification of blood and blood products, stating that laboratories should document the accuracy of bar codes before putting the systems into use, and as a continuing part of quality assurance while the systems are in use.

Response: We agree with the commenter that the accuracy and ongoing reliability of bar code systems used for the identification of blood and blood products is an important quality issue for laboratories that use them. Laboratories involved in collecting, processing, dating, labeling, testing, and distributing blood and blood products are required to conform to the FDA requirements for blood and blood products at 21 CFR parts 606, 640, 21 CFR 610.40, and 610.53. Specifically, 21 CFR 606.121: Container label, permits the use of container labels that bear encoded information in the form of machine-readable symbols approved for use by the Director, Center for Biologics Evaluation and Research, FDA, and refers to FDA's ''Guideline for Uniform Labeling of Blood and Blood Components,'' that addresses blood product labeling requirements, including standards for bar codes. Also, 21 CFR 606.140 requires the laboratory to have control procedures that provide for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.

Comment: A laboratory surveyor asked why CLIA personnel are responsible for surveying large sections of the FDA's regulations. Since CLIA is a self-funded program, the commenter wondered if the FDA reimbursed the CLIA program for these services.

Response: The commenter is correct in questioning the role of the CLIA surveyors' inspection responsibilities. We have corrected the citations from 21 CFR to specify in 42 CFR part 493 the exact requirements that must be met under the CLIA regulations. The revised citations are now at §§ 493.1105(a)(1)(i), 493.1271(a)(1) and (b). When reviewed, the actual time expended surveying sections of the FDA's regulation was minimal. Sister agencies such as the FDA and CMS frequently assist one another without charge when expenditures to provide such assistance are *de minimis.*

Subpart M—Personnel for Moderate Complexity (Including the Subcategory) and High Complexity

In the February 28, 1992 final rule with comment period, the personnel requirements are located in subpart M and include qualification requirements for individuals to direct a laboratory performing high complexity testing. A phase-in period was provided for individuals with a doctoral degree to obtain board certification. In response to the publication of the date extension rules, we received comments suggesting that we develop alternative provisions to qualify individuals with a doctoral degree on the basis of laboratory training or experience, instead of requiring board certification. On December 28, 2001, we published a proposed rule in the **Federal Register** (66 FR 67163) that included provisions to end the phase-in period and revise and expand the qualifications required for an individual with a doctoral degree to direct a laboratory performing high complexity testing.

Following publication of the proposed rule, we received 113 comment letters, which contained approximately 300 comments. Of these, 168 comments agreed with one or more provisions in the proposed rule, 120 comments disagreed with at least one of the provisions, 6 comments addressed the education requirements, and 1 comment reflected misinterpretation of the proposed requirements. Fifty-three of the 113 comment letters specifically addressed qualification requirements for directors of laboratories performing histocompatibility testing.

Specific comments received and responses to comments regarding the proposed rule are set forth below.

Comment: The majority of the comments on the first provision (at the proposed and former § 493.1443(b)(3)(i)) agreed with requiring board certification

as a qualification requirement for individuals having a doctoral degree to serve as high complexity laboratory directors. These commenters emphasized the role of board certification in ensuring that individuals have specific training and experience, as well as uniform and broad-based clinical knowledge, skills and competencies. In addition, at the CLIAC meeting held on January 30, 2002 through January 31, 2002, CLIAC expressed strong support for board certification for laboratory directors and suggested the recent efforts of the boards to provide more flexible routes to certification would allow more individuals to meet the certification requirements. CLIAC and other commenters also felt that the documentation of continuing education required for retaining board certification is essential in ensuring that individuals maintain the professional abilities needed to direct laboratories that provide services in the multifaceted, constantly changing high complexity testing category. The few comments opposed to board certification indicated certification does not ensure the performance of individuals and that employee skill validation is the responsibility of the employer. These commenters also noted the absence of evidence documenting that certified individuals perform better than noncertified individuals.

Response: We agree with the comments supporting board certification and are maintaining the former requirements at § 493.1443(b)(3)(i) requiring board certification as one of the pathways for qualifying individuals with a doctoral degree as directors of laboratories performing high complexity testing. Although certification does not provide absolute assurance that individuals will effectively fulfill the responsibilities required of directors, it is a recognized benchmark of competency and an appropriate mechanism for qualifying individuals to serve as laboratory directors. In addition, the ongoing continuing education required by each of the HHS-approved boards to retain certification helps ensure these individuals maintain a current knowledge base.

Comment: A State Health Department and one laboratory professional organization requested that all HHS-approved boards and the criteria for board approval be listed in the regulations. One of these commenters asked whether the phrase ''* * * be certified and continue to be certified * * *'' included in the proposed rule at § 493.1443(b)(3)(i) means that HHS will require board recertification when required by an HHS-approved board. In addition, a few commenters disagreed with board recertification.

Response: A total of eight certification boards have been approved by HHS. Four boards are listed in the former regulations at § 493.1443(b)(3)(i): The American Board of Medical Microbiology; the American Board of Clinical Chemistry; the American Board of Bioanalysis; and the American Board of Medical Immunology. On July 8, 1996, we published a notice in the **Federal Register** (61 FR 35736), that announced HHS approval of two boards: The American Board of Histocompatibility and Immunogenetics and the American Board of Medical Genetics. In this final rule, we are announcing HHS-approval of two additional boards: the National Registry for Clinical Chemistry at the doctoral level and the American Board of Forensic Toxicology. However, in this final rule, we are deleting the reference at § 493.1443(b)(3)(i) to the specific boards approved by HHS. Currently, all HHS-approved boards are listed on the Internet at *http://www.cms.hhs.gov/clia/dirc/con.asp.* In the future, boards approved by HHS will also be listed in Appendix C of the State Operations Manual (CMS Pub. 7), subpart M. Removing the list of approved boards from the regulations and placing the list in Appendix C will allow greater flexibility to update the list of HHS-approved boards.

In response to the comments suggesting that the criteria for determining HHS-approval of certification boards be included in the regulations, we do not believe that regulations, which specify standards that must be met by covered entities, should include details of an administrative process. All boards approved by HHS have been determined to have comparable certification requirements. In the ''Conditions for Coverage of Services of Independent Laboratories'' published in the September 19, 1974 **Federal Register** (39 FR 33693), the laboratory director qualification requirements included provisions for qualifying individuals with a doctoral degree. One option was certification by one of three boards (American Board of Medical Microbiology, the American Board of Clinical Chemistry, and the American Board of Bioanalysis). Subsequently, all boards approved by HHS have been determined to have certification requirements comparable to those three boards originally recognized. Any board may request HHS approval by submitting their request for board certification to CMS. This information will be evaluated to determine if the board's certification requirements are comparable to those currently approved boards.

With respect to requiring recertification, it was always the intent of the former regulations, that individuals with a doctoral degree qualifying under § 493.1443(b)(3)(i) must be, and continue to be, certified by an HHS-approved board. If a board requires recertification and an individual fails to recertify and loses board certification, this individual would no longer meet the director qualification requirement at § 493.1443(b)(3)(i). In this final rule, and as proposed in the December 28, 2001 proposed rule, we are revising the language at § 493.1443(b)(3)(i) for clarification.

Comment: A number of comments agreed with the second provision (at proposed § 493.1443(b)(3)(ii)) allowing individuals having a doctoral degree, who are serving or have served as directors of laboratories performing high complexity testing under the current regulations' phase-in provision, to continue to qualify without obtaining board certification. However, a few commenters felt this provision should be temporary, with a date specified by which board certification would be required to maintain qualification. One commenter urged that a date be established (and not extended) to conclude this qualification provision. A State Health Department interpreted the requirements in this provision to mean that a total of 4 years of experience is required, and that the training and experience and director and/or supervisory experience cannot be gained concurrently. This commenter also suggested this experience be postdoctoral experience.

Response: We agree the second proposed qualification provision is needed to allow (''grandfather'') individuals who have served or are currently serving as directors of high complexity testing to continue to serve. We also agree that a date needs to be specified to conclude this qualification pathway and the training and experience requirements clarified; however, we do not agree that the training and experience must be postdoctoral. We believe laboratory training and experience obtained while an individual is working toward obtaining a doctoral degree is pertinent and appropriate, and should be considered as meeting the requirement.

In this final rule, at § 493.1443(b)(3)(ii), we are specifying February 24, 2003, as the effective date

for this final rule's personnel qualification requirements, and we are clarifying the training and experience requirements individuals must meet. To ensure a smooth transition to the new provisions for directors of high complexity testing who are not board certified (but who have doctoral degrees), we will not be holding facilities out of compliance with the provisions of the rule concerning directors who are not board certified until the effective date of this new rule, to the extent the facilities are otherwise in compliance with the requirements for laboratory directors. Individuals must, therefore, as of February 24, 2003, have at least 2 years of training or experience, or both; and 2 years of experience directing or supervising high complexity testing.

Comment: Several commenters (including one laboratory professional organization and one certification board) felt continuing education should be added as a requirement to the second proposed provision.

Response: We acknowledge that continuing education is important; however, the proposed rule did not include a continuing education component for this provision. In addition, when ''grandfathering'' individuals who are serving or who have served in a particular position, minimum qualification requirements are considered so as not to disenfranchise these individuals. Finally, while regulations specify minimum requirements, States, accreditation organizations, and certification boards may establish more stringent requirements.

Comment: The majority of the commenters were opposed to including the third provision (at proposed § 493.1443(b)(3)(iii)). While there was general agreement that training and experience is essential for direction of high complexity testing, a few commenters (including a certification board and a laboratory professional organization) noted that training and experience vary greatly and it would be inappropriate to use training and experience as sole criteria to qualify individuals with a doctoral degree to direct high complexity testing. CLIAC also recommended that this provision be eliminated because it would not provide adequate documentation of the knowledge and skills needed for directorship of high complexity testing, lacks a mechanism to ensure continued competency, and is not commensurate with the high complexity laboratory director responsibilities. Several commenters noted that this proposed qualification pathway might result in an increase in the quantity of individuals qualified to direct high complexity testing at the expense of quality, which is in part attributed to a competent workforce. Although a few commenters agreed with this proposed provision to provide qualification specifications based on training and experience in lieu of board certification, they suggested revisions to make the provision more stringent and felt continuing education should be added to ensure that individuals maintain competency.

Response: We agree with the comments expressing disagreement with the third proposed qualification pathway and are not including it in this final rule. Although high complexity procedures comprise less than 20 percent of the laboratory procedures categorized, these are the most complex tests requiring a broad-based knowledge and the highest skills to fulfill the director responsibilities (formerly at § 493.1445) and ensure quality testing. Therefore, we believe the knowledge and training of a high complexity laboratory director with a doctoral degree can best be demonstrated through board certification. In addition, in the former regulations, we provided phase-in qualification requirements that allow individuals with a doctoral degree to qualify based on training and experience in lieu of board certification until the specified expiration date. As mentioned earlier, on five separate occasions, we extended the phase-in provision to allow time for directors who were not board certified to complete the certification requirements and for HHS to review and approve certification boards. During the 10 years the phase-in provision has been in affect, HHS has approved five additional boards and we believe sufficient time has been provided for individuals to become aware of the board certification requirement. Moreover, recent efforts of certification boards have provided additional routes to certification, allowing more individuals to meet the certification requirements.

In this final rule, board certification will be required for an individual with a doctoral degree seeking to become a high complexity laboratory director on and after February 24, 2003. However, as previously mentioned, we are allowing individuals, who qualified under the phase-in provision and are now serving or have served as directors of laboratories performing high complexity testing, to continue to serve as laboratory directors.

Comment: A few commenters disagreed with requiring a doctoral degree as the minimum education requirement for directors of laboratories performing high complexity testing. They suggested that individuals with an appropriate master's degree and progressive experience in the clinical laboratory (5 to 10 years) should be able to qualify.

Response: We believe the doctoral degree is an appropriate minimum education requirement for directors of laboratories performing high complexity testing. It is commensurate with the responsibilities of a high complexity laboratory director, as specified in the former regulations at § 493.1445, and consistent with the education requirements and responsibilities specified for the other laboratory personnel categories described in subpart M of the regulations.

Comment: Several commenters from local, county, and public health officials in a State disagreed with the doctoral degree requirement and cited the State Code that allows an individual with a baccalaureate or master's degree to direct a public health laboratory. The commenters noted that although the public health laboratories currently have a director who meets the CLIA regulations, many of these directors qualified under the former regulations at § 493.1443(b)(5), the ''grandfather'' provision that qualifies individuals if on or before February 28, 1992, they were qualified as a director under State law. Many of these directors will retire within 5 years.

Response: For the reasons stated previously, we believe the education requirements for directors of high complexity laboratories are appropriate and should not be lowered. In addition, as noted by the commenters, the February 28, 1992 final rule with comment period included a grandfather provision that qualified individuals that were serving as laboratory directors under State law on or before that date. We also provided a phase-in provision, which allows individuals with doctoral degrees time to obtain board certification by the specified expiration date. The phase-in provision was extended on multiple occasions and during this 10-year period HHS has approved five additional boards. We believe sufficient time has been provided for individuals to become aware of the requirements. In this regard, the State revised its statutes in a February 18, 1998 amendment and now requires any city or county public health laboratory and its personnel to comply with the CLIA regulations.

Comment: One commenter thought the proposed regulation would only allow physicians to serve as directors of laboratories performing high complexity testing.

Response: Although physicians with certain training or experience are qualified to serve as directors of laboratories performing high complexity testing, the notice of proposed rulemaking only included proposed revisions to the qualification requirements by which an individual with a doctoral degree may serve as a director of a laboratory that performs high complexity testing.

Comment: We received numerous comments on the qualification requirements for directors of laboratories performing histocompatibility testing. The majority of this group of commenters, which included the American Society of Histocompatibility and Immunogenetics (ASHI), and the American Board of Histocompatibility and Immunogenetics (ABHI), were in support of requiring specific histocompatibility training and experience for directors of laboratories performing histocompatibility testing. Specifically, they were in favor of requiring individuals with a doctoral degree to either meet the histocompatibility technical supervisor requirements specified in the former regulations at § 493.1449(o) and be certified by ABHI; or be serving or have served as a director of a histocompatibility laboratory and meet the histocompatibility technical supervisor requirements at § 493.1449(o). Opposing comments expressed concern that ASHI's proposal would exclude qualified individuals currently serving as directors of laboratories performing histocompatibility testing and is unnecessarily restrictive in an effort to protect the employment of those individuals who possess ABHI certification.

Response: We do not agree that the qualifications for directors of laboratories performing histocompatibility testing, which is categorized as high complexity testing, need to be revised to include specific histocompatibility training and education requirements. We note the revisions suggested by ASHI would establish higher director qualification requirements for individuals having a doctoral degree than for physicians who direct laboratories performing histocompatibility testing. In addition, these suggested changes to the qualifications for directors of laboratories performing histocompatibility testing would be inconsistent with the former qualifications required to direct laboratories performing other testing specialties. Although the commenters maintained that histocompatibility is highly complex and requires specialized skills for direction, other specialty areas (for example, cytogenetics and pathology) are also complex and require specialized technical expertise. Under the CLIA regulations, the requirements for specialty training and experience are included under the qualification requirements for the technical supervisor, which vary depending on the specialty of service. The December 28, 2001 proposed regulation did not include technical supervisor requirements, and we are not making any changes to the former requirements for technical supervisors.

In addition, several commenters mistakenly thought that having the director meet the histocompatibility technical supervisor requirements would eliminate the need for two individuals. Two individuals are only needed when a particular individual is unable to meet both the laboratory director and histocompatibility technical supervisor qualification requirements.

Finally, while regulations specify the minimum requirements for compliance, accreditation organizations may establish higher requirements for laboratory accreditation.

Subpart P—Quality Assurance for Moderate Complexity (Including the Subcategory), High Complexity Testing, or Any Combination of These Tests

Following publication of the February 28, 1992 final rule with comment period, we received approximately 25 comments in reference to subpart P. The comments were in response to the requirements for enforcement of a written quality assurance policy. The laboratory's policy was required to address the ongoing and overall monitoring and evaluation of the quality of the total testing process and the laboratory's policies and procedures, identifying and correcting problems to ensure the accurate, reliable, and prompt reporting of test results, and to ensure the adequacy and competency of the staff. Over half of the comments received agreed with most of the requirements. Approximately 25 percent of the comments disagreed with some of the requirements or offered specific revised language.

Specific comments and responses regarding subpart P are set forth below.

Comment: One commenter suggested that the CLIA regulation specify who has primary responsibility for QA activities by adding a statement, for example, ''The laboratory director is responsible for ensuring that a quality assurance program is established and maintained.''

Response: We agree with the commenter. A requirement already appears at §§ 493.1407(e)(5) and 493.1445(e)(5), moderate complexity and high complexity laboratory director responsibilities, respectively, and states ''The laboratory director must ensure that the quality control and quality assessment programs are established and maintained to ensure the quality of laboratory services provided and to identify failures in quality as they occur.'' In addition, we are now providing an introduction at § 493.1200, subpart K that provides an overview of what quality systems include, the importance of ongoing assessment of these systems, and the laboratory's responsibility for establishment and maintenance of appropriate policies and procedures. The term ''quality assurance'' is synonymous with the term ''quality assessment.'' In addition, we are also making conforming changes (''assessment'' replaces ''assurance'') where appropriate.

Comment: One commenter suggested adding text at § 493.1709, Comparison of test results, that would acknowledge the role the manufacturer may have in verifying the accuracy and reliability of test results at least twice a year. Other commenters suggested language to clarify that tests not included under subpart I, performed by the laboratory at various (multiple) testing sites, must also be evaluated twice a year.

Response: Manufacturers are not precluded from providing services to laboratories to assist in verification of the accuracy and reliability of test procedures. However, it is ultimately the responsibility of the laboratory to develop and implement protocols for the biannual evaluation and comparison of test results obtained using the different methodologies and instruments employed by the laboratory and various testing sites the laboratory may have (for example, central laboratory, satellite laboratories, point-of-care testing). In addition, the laboratory must, twice a year, verify the accuracy of any test it performs that is not listed in subpart I. Therefore, we believe the requirements, formerly at § 493.1709 (now at §§ 493.1281 and 493.1236), clearly state the testing that must be evaluated and the requirements remain unchanged.

Comment: We received a comment agreeing with the requirement at § 493.1707, Proficiency testing assessment. The commenter stated that all proficiency testing (PT) results that were not correct should be investigated. Another commenter stated that all regulated analytes must be graded or the PT program must notify HHS and the

affected laboratory of any challenge, analyte, or test method for which it cannot produce a grade and the reasons why grading is not possible. A few commenters strongly disagreed with the practice of assigning a 100 percent score to PT analytes when the laboratory has not earned the score. The commenters stated that this practice penalizes laboratories that have correctly performed testing on all PT samples and causes laboratories that receive false representation of a grade to believe their test performance is exemplary, when it has not been comparatively evaluated. Additionally, laboratory testing problems that exist are not identified; therefore, no corrective actions are taken.

Response: Individual responses to the above comments are as follows:

• We agree with the commenter and are retaining the requirement formerly at § 493.1707 (now at § 493.1236) for the laboratory to review and evaluate results obtained on proficiency testing. PT result review is part of the QA process.

• We anticipate all regulated analytes (those listed in subpart I) will be graded by approved PT programs. The commenter is correct that, in some cases, not all challenges have been graded. Occasionally, as new methodologies or new instrumentation are developed for tests listed in subpart I, PT material is not always available or compatible with the new methods or instruments. In order to ensure that laboratories using new methodologies or instruments evaluate their performance, we are (now at § 493.1236(c)(2)) requiring laboratories to verify twice annually the accuracy of tests listed in subpart I for which compatible PT material is not available from approved programs.

• We agree with the commenter's recommendation to require PT programs to notify the laboratories and HHS of any challenge, analyte, or test method that cannot produce a grade and the reasons why grading is not possible. As CDC and CMS perform the annual review of PT programs required by the CLIA statute, programs must submit an annual report and, if needed, an interim report that identifies any previously unrecognized sources of variability in kits, instruments, methods, or PT samples that adversely affect the programs' ability to evaluate laboratory performance. This requires PT programs to report problems to CMS. We are also requiring programs to notify laboratories (on the laboratory's PT results report) of exceptions and/or problems that precluded an analyte from being graded.

• We appreciate the commenters' concerns regarding false grading; however, there are reasons why false grading occurs. Almost all areas of testing under PT must be graded on an overall basis, that is, each analyte score under a subspecialty or specialty is averaged on each testing event to provide the laboratory with an overall subspecialty or overall specialty score. In order to determine an overall score, each analyte must receive a numerical score to allow the overall specialty or subspecialty to be graded. The circumstances that a PT program may assign an analyte score that does not reflect the laboratory's true test performance include: (1) Analyte evaluation does not produce at least 90 percent agreement among participant or referee laboratories that is required by regulation (the laboratory receives 100 percent score); (2) laboratory did not participate in the testing event (the laboratory receives zero percent score); or (3) laboratory's PT results were received after the cut-off date for receipt (the laboratory receives a score of zero percent for the late return of results). In response to the commenters' concerns, we are now requiring at § 493.1236(a)(2) that the laboratory verify the accuracy of the analytes for which a grade was assigned that did not reflect its true testing performance.

V. Provisions of the Final Rule

In response to public comments on the final rule with comment period and to provide policy clarifications, we made a number of changes in this final rule, which are summarized as follows:

Subpart A—General Provisions (Definitions)

• We added at § 493.2 the definitions for the terms ''calibration,'' ''calibration verification,'' ''FDA-cleared or approved test system,'' ''reportable range,'' and ''test system.''

• We revised § 493.3(b)(3) to remove the words ''National Institutes on Drug Abuse (NIDA)'' and add, in their place, the agency's new name, ''Substance Abuse and Mental Health Services Administration (SAMHSA).''

• We revised § 493.20 by removing the reference to ''subpart P'' and adding the cross reference to ''§ 493.1773.''

• We revised § 493.25 by removing the reference to ''subpart P'' and adding the cross reference to ''§ 493.1773.''

Subpart C—Registration Certificate, Certificate for Provider-performed Microscopy Procedures, and Certificate of Compliance

• We revised § 493.43(a) by removing the words ''tests of moderate complexity (including the subcategory) or high complexity, or any combination of these tests,'' and adding, in their place, the words ''nonwaived testing.''

• We revised § 493.45 by removing the reference to ''subpart P.''

• We revised § 493.47 by removing the reference to ''subpart P''.

• We revised § 493.47(c)(3) by removing the cross reference to ''§ 493.1776'' and adding, in its place, a cross reference to ''§§ 493.1773'' and ''493.1775.''

• We revised § 493.49 by removing the reference to ''subpart P.''

Subpart F—General Administration

• We added at § 493.643(c)(3)(ix) the word ''Clinical before the word ''Cytogenetics'' to correct a technical error. The word was inadvertently omitted from the final rule with comment period.

Subpart H—Participation In Proficiency Testing for Laboratories Performing Nonwaived Testing

• We revised the heading of subpart H to read ''Participation In Proficiency Testing for Laboratories Performing Nonwaived Testing.''

• We revised ''§ 493.801(a)(2)(ii)'' by removing the cross reference to ''§ 493.1709'' and adding, in its place, ''§ 493.1236(c)(1).''

• We revised ''§ 493.803(a)'' by removing the words ''tests of moderate complexity (including the subcategory), and/or high complexity'' and adding, in their place, the words ''nonwaived testing.''

• We revised the heading of § 493.807 to read ''Condition: Reinstatement of laboratories performing nonwaived testing.''

Subpart I—Proficiency Testing Programs for Nonwaived Testing

• We revised the heading of subpart I to read ''Proficiency Testing Programs for Nonwaived Testing.''

• We revised this subpart by changing the 90 percent consensus requirement to 80 percent consensus.

• We revised § 493.945 by removing the cross reference to ''§ 493.1257'' and adding in its place §§ 493.1105(a)(7)(i)(A) and 493.1274(f)(2).''

Revisions to Subpart J and K

As stated in section II of this preamble (Highlights and Organization of Final Rule), we have consolidated and reorganized the requirements formerly in Subpart J—Patient Test Management for Moderate Complexity (Including the Subcategory), High Complexity, or Any Combination of These Tests, Subpart K—Quality Control for Tests of Moderate Complexity (Including the

Subcategory), High Complexity, or Any Combination of These Tests, and Subpart P—Quality Assurance for Moderate Complexity (Including the Subcategory) or High Complexity Testing, or Any Combination of These Tests, into a new Subpart J—Facility Administration for Nonwaived Testing, and Subpart K—Quality Systems for Nonwaived Testing. Below, we have only set forth substantive revisions to subparts J and K.

Subpart J—Facility Administration for Nonwaived Testing

- We revised the heading of subpart J to read Facility Administration for Nonwaived Testing.
- We revised subpart J to consist of §§ 493.1100 through 493.1105.
- We specified now at § 493.1100 that laboratories performing nonwaived testing must meet the applicable standard level requirements in §§ 493.1101 through 493.1105.
- We added the requirement now at § 493.1101(c) that laboratories must comply with Federal, State, and local requirements concerning laboratories and ensure that adequate safety precautions are in place to provide protection from laboratory hazards.
- We revised the language now at § 493.1101(d) (formerly at § 493.1204(b)) requiring safety procedures to be accessible rather than posted.
- We clarified the record keeping requirements now at § 493.1101(e) for laboratories to store and maintain records in a manner that ensures proper preservation. This clarification applies to the requirements now at § 493.1771(c) and (d), and former §§ 493.1105, 493.1107, and 493.1221 introductory text.
- We removed the language formerly at § 493.1103(c) regarding laboratories providing oral instruction to patients as a supplement to written instructions, when appropriate.
- We clarified the requirement now at § 493.1103(d) (formerly at § 493.1271) that the facility must report transfusion reactions to the laboratories and, as appropriate, to Federal and State authorities.
- We revised the language now at § 493.1105(a)(3)(i) (formerly at § 493.1221) to specify that the laboratory must retain records of test system performance specifications that the laboratory establishes or verifies under § 493.1253 for the period of time the laboratory uses the test system but no less than 2 years.
- We revised the language now at § 493.1105(a)(3)(ii) (formerly § 493.1107 introductory text) and § 493.1105(a)(6)(i) (formerly § 493.1109 introductory text) to specify the record retention requirements for immunohematology and blood and blood products to ensure consistency with the FDA requirements.
- We revised the requirement now at § 493.1105(a)(6) (formerly § 493.1109 introductory text) to remove the words ''exact duplicate'' and specify that the laboratory must be able to retrieve a copy of the original report.

Subpart K—Quality Systems for Nonwaived Testing

- We revised the heading of subpart K to read ''Quality Systems for Nonwaived Testing.''
- We revised subpart K to consist of §§ 493.1200 through 493.1299.
- We revised the introductory text now at § 493.1200 to provide an overview of quality systems, including the importance of ongoing assessment of these systems, and the laboratory's responsibility for establishment and maintenance of appropriate policies and procedures.
- We removed the lead-in paragraph formerly at § 493.1201(a) explaining the division between general QC and the QC for the specialties and subspecialties.
- We removed the requirement formerly at § 493.1201(a)(1) regarding the clearance process for alternative QC procedures that were never established by the FDA.
- We removed the requirement formerly at § 493.1203 regarding the clearance process for moderate complexity testing.
- We redesignated the requirement formerly at § 493.1205 regarding test methods, equipment, instrumentation, reagents, materials, and supplies. We incorporated the majority of these provisions into § 493.1252. The requirements formerly at § 493.1205(b) are now at § 493.1101(b) and the biologic product dating requirements formerly at § 493.1205(e) are now at § 493.1271(b).
- We removed the requirement formerly at § 493.1213(b)(1) regarding the QC clearance process for the manufacturer's process for verification of performance specifications for new patient testing devices introduced by the laboratory.
- We removed the requirement formerly at § 493.1215(a)(1) regarding the CLIA QC clearance process for maintenance of equipment, instruments, and test systems.
- We removed the requirement formerly at § 493.1217(a) regarding the CLIA QC clearance process for use of the manufacturer's instructions for calibration and calibration verification procedures.
- We removed the requirement formerly at § 493.1217(b)(2)(ii)(B)(1) (calibration verification requirement) regarding use of calibration materials traceable to a reference method or reference material of known value to allow flexibility in choosing material for calibration verification.
- We removed the requirements formerly at § 493.1225, the Condition of Microbiology, as it is a duplicate of the requirements under the Conditions of Bacteriology, Mycobacteriology, Mycology, Parasitology, and Virology, now at §§ 493.1201, 493.1202, 493.1203, 493.1204, and 493.1205, respectively.
- We clarified the requirement now at § 493.1236 (formerly at § 493.1707) that laboratories must verify the accuracy of any analyte, specialty, or subspecialty when it is assigned a proficiency testing score that does not reflect laboratory test performance.
- We added the requirement now at § 493.1236(c)(2) that laboratories verify twice annually the accuracy of tests listed in subpart I for which compatible PT material is not available from approved PT programs.
- We removed the requirement formerly at § 493.1237, the Condition of Diagnostic Immunology, as it is a duplicate of the requirements under the Conditions of Syphilis Serology and General Immunology now at §§ 493.1207 and 493.1208, respectively.
- We revised the language now at § 493.1241(b) (formerly at § 493.1105) to clarify that an oral request for laboratory tests is permitted only if laboratory requests written or electronic authorization for testing within 30 days of the oral request and documents the efforts made to obtain a written or electronic authorization.
- We revised the language now at § 493.1241(c)(3) (formerly at § 493.1105(e) and (f)) to specify that the test requisition must solicit the patient's sex and age or date of birth.
- We added the requirement now at § 493.1241(c)(5) (formerly § 493.1105(f)) that the laboratory must ensure that the test requisition solicits the source of the specimen when appropriate.
- We revised the language now at § 493.1241(c)(7) (formerly at § 493.1105(e)) removing the age or date of birth requirement for Pap smear requisitions because it is now a requirement for all test requisitions at § 493.1241(c)(3).
- We revised the requirement now at § 493.1241(e) (formerly § 493.1701) to provide clarification that if the laboratory transcribes or enters test requisition or authorization information into a record system or laboratory information system, the laboratory must

ensure that the information is transcribed or entered accurately.

• We revised the requirement now at § 493.1242(a)(3) (formerly § 493.1105(f)) clarifying that the specimen source requirement, when appropriate, is part of the laboratory's submission, handling, and referral procedures.

• We removed the requirement formerly at § 493.1243, the Condition of Chemistry, as it is a duplicate requirement under the Conditions of Routine Chemistry at § 493.1210, Urinalysis at § 493.1211, Endocrinology at § 493.1212, and Toxicology at § 493.1213.

• We clarified the requirement now at § 493.1251(b)(13) (formerly at § 493.1211(b)(14)) that the procedure manual must include in the test procedure the laboratory's system for entering results in the patient record and reporting patient results including the protocol for reporting panic or alert values, when appropriate.

• We revised the language now at § 493.1251(d) (formerly at § 493.1211(d)) to provide that procedures and changes in procedures must be approved, signed, and dated by the current laboratory director before use.

• We revised the language now at § 493.1252(b) (formerly §§ 493.1202(c)(1) and 493.1205(c)) to specify that the laboratory's criteria for storage of reagents and specimens and test system operations must be consistent with the manufacturer's instructions, when available.

• We revised the language now at § 493.1253(a) (formerly at § 493.1213(a)) to provide that laboratories are not required to verify or establish performance specifications for any test system used by the laboratory before April 24, 2003.

• We revised the language now at § 493.1253(b)(1) (formerly at § 493.1213(b)(2)) by adding the words ''FDA-cleared or approved test system'' to the requirements regarding verification of performance specifications.

• We revised the heading now at § 493.1254 (formerly § 493.1215) to read ''Maintenance and function checks.''

• We revised the language now at § 493.1254(a)(2) (formerly at § 493.1215(b)(2)(ii)) regarding function checks by removing the word ''laboratory'' and adding, in its place, the word ''manufacturers.''

• We clarified the requirement now at § 493.1254(a)(2) (formerly at §§ 493.1202(c)(1) and 493.1215(b)(2)(ii)) to require that function checks be within the manufacturer's established limits before conducting patient testing.

• We removed the requirement formerly at § 493.1255, the Condition of Pathology, as it is a duplicate requirement under the Conditions of Histopathology, Oral Pathology and Cytology now at §§ 493.1219, 493.1220, and 493.1221, respectively.

• We revised the language now at § 493.1256 by removing the mandatory concurrent control testing requirements formerly at §§ 493.1237 Diagnostic immunology; 493.1239 Syphilis serology; and 493.1241 General immunology. We now require two levels of QC materials once each day of testing.

• We revised the language now at § 493.1256(d) (formerly at § 493.1218(b)) reducing the requirement by removing the specialty-specific control requirements (formerly at § 493.1253(b)) for automated hematology analyzers. We now require two levels of control materials once each day of testing.

• We revised the language now at § 493.1256(d)(3) (formerly at § 493.1218(b)) to clarify that QC materials are assayed or examined each day of patient testing.

• We revised the requirement now at § 493.1256(d)(3) for hematology by reducing the required frequency for control testing (formerly at § 493.1253(b)) from once each 8 hours of operation to once each day of testing.

• We added the requirement now at § 493.1256(d)(3)(v) that the laboratory must use a control system capable of detecting reaction inhibition when performing molecular amplification procedures in which inhibition is a significant source of false negative results.

• We removed the term ''drug abuse screening'' at § 493.1256(d)(4)(i), and added the term ''all known substances or drug groups'' identified and reported by the laboratory to accommodate the wider use of the technology.

• We revised the language now at § 493.1256(d)(5) (formerly at § 493.1218(b)(3)) to clarify that the laboratory must for each electrophoretic procedure, include, concurrent with patient specimens, at least one control material containing the substances being identified or measured.

• We revised the language now at § 493.1256(e)(2) (formerly § 493.1218(f)(2)) to clarify the use of staining materials.

• We clarified the use of calibration materials now at § 493.1256(d)(9) (formerly at § 493.1218(h)(2)) to provide that calibration material used as a control material must be from a different lot number than that used to establish a cut-off value or to calibrate the test system.

• We revised the requirement now at § 493.1261 by incorporating the bacteriology requirements formerly at § 493.1227.

• We revised the language now at § 493.1261 (formerly § 493.1227), reducing the requirements by removing the reference to specific control requirements in the subspecialty of bacteriology.

• We revised the requirement now at § 493.1262 by incorporating the mycobacteriology requirements formerly at § 493.1229.

• We added a requirement in mycobacteriology now at § 493.1262(a) (formerly § 493.1229(a)) for an acid fast control organism that produces a negative reaction.

• We revised the requirement now at § 493.1263 by incorporating the mycology requirements formerly at § 493.1231.

• We revised the requirement now at § 493.1263(a) (formerly at § 493.1218(f)(2)). We reduced the requirement to QC certain staining materials each day of use to only checking each batch, lot number, and shipment of lactophenol cotton blue when prepared or opened for intended reactivity.

• We revised the requirement now at § 493.1263(b) (formerly § 493.1213(d)) by reducing the requirement for daily testing to merely testing each batch of media and each lot number and shipment of antifungal agents before or concurrent with initial use.

• We revised the requirement now at § 493.1264 by incorporating the parasitology requirements formerly at § 493.1233.

• We revised the requirement now at § 493.1265 by incorporating the virology requirements formerly at § 493.1235.

• We removed the requirement formerly at § 493.1265(a)(10) that required the laboratory to use specific techniques such as mixed lymphocyte cultures to determine HLA Class II incompatibilities.

• We removed the requirement formerly at § 493.1265(a)(13) that required histocompatibility testing personnel to evaluate unknowns on a monthly basis because it is duplicative of the laboratory director responsibilities at § 493.1445(e).

• We revised the requirement now at § 493.1267 by incorporating the routine chemistry requirements formerly at § 493.1245.

• We revised the language now at § 493.1267(b) (formerly at §§ 493.1245(c) and (d)) by removing reference to the words ''calibration and calibration material'' from the blood gas requirements. However, we allow

calibration material as a control material provided it is from a different lot number than that used to calibrate the test system or establish a cut-off.

• We revised the requirements now at § 493.1269 by incorporating the hematology requirements formerly at § 493.1253.

• We revised the requirement now at § 493.1271 by incorporating the immunohematology requirements formerly at §§ 493.1239(e), 493.1241(d), 493.1269, 493.1273, 493.1275, 493.1283, and 493.1285.

• We revised the requirement now at §§ 493.1271(a)(1) and (b) (formerly §§ 493.1269(a) and 493.1273) to cite the specific 21 CFR requirements that must be met under the CLIA regulations.

• We revised the requirement now at § 493.1273 by incorporating the histopathology requirements formerly at § 493.1259.

• We added a requirement at § 493.1273(a) (formerly at § 493.1259) that the laboratory must check immunohistochemical stains for positive and negative reactivity each time of use in order to be consistent with the general QC requirements at § 493.1256(e)(3).

• We revised the language now at § 493.1273(c) (formerly at § 493.1259(b)) to add that an individual who has successfully completed a training program in neuromuscular pathology approved by HHS may examine and provide reports for neuromuscular pathology.

• We revised the requirement now at § 493.1274 by incorporating the cytology requirements formerly at § 493.1257.

• We revised the language now at § 493.1274(d)(2)(iii) (formerly at § 493.1257(b)(2)) by removing the reference to gynecologic slides from the 200-workload limit that applies only to nongynecologic slides.

• We revised the language now at § 493.1274(e)(1) (formerly at 493.1257(c)(1)) by removing the requirement that a technical supervisor review cases categorized as reactive and reparative changes.

• We revised the requirement now at § 493.1276 (formerly at § 493.1267) by incorporating the clinical cytogenetics requirements.

• We clarified the requirement at § 493.1276(a) (formerly §§ 493.1107 and 493.1267(c)) by specifying that the laboratory must have policies and procedures for ensuring accurate and reliable patient specimen identification for karyotypes.

• We revised the requirement now at § 493.1276(b)(2) (formerly at § 493.1267(b)) to specify that the laboratory must have records that document that the resolution used was appropriate for the type of tissue or specimen, and the type of study required based on the clinical information provided to the laboratory.

• We revised the language now at § 493.1276(c) (formerly at § 493.1267(a)) by removing the requirements pertaining to the performance of X and Y chromatin counts for sex determination and requiring full chromosome analysis for sex determination.

• We revised the language now at § 493.1276(d) (formerly at § 493.1267(d)) by removing the reference to the words ''appropriate nomenclature'' and specifying that the laboratory report must use the International System of Cytogenetic Nomenclature.

• We revised the requirement now at § 493.1278 by incorporating the histocompatibilty requirements formerly at § 493.1265.

• We added the requirement now at § 493.1278(a)(3) that reagent specificity is required when reagent typing sera inventory is prepared in-house.

• We added requirements now at § 493.1278(b)(1) that the laboratory must use a technique that is established to optimally define, as applicable, HLA Class I and II specificity.

• We added requirements at § 493.1278(d)(1) and (d)(2) to specify that the laboratory must use a technique that detects HLA specific antibody with a specificity equivalent or superior to that of the basic complement-dependent microlymphocytotoxicity assay, and use a method that distinguishes antibodies to HLA class II antigens from antibodies to Class I antigens.

• We revised the language now at § 493.1278(d)(4) and (d)(5) (formerly at 493.1265(a)(2)(ii) and (a)(8)(i)) to require laboratories to make a reasonable attempt to have available monthly serum specimens for periodic antibody screening and crossmatch, and have available and follow a written policy consistent with clinical transplant protocols for the frequency of performing antibody screening.

• We added the requirement now at § 493.1278(d)(7) to specify that for antibody screening, the laboratory must, as applicable, have available, and follow criteria and procedures for antibody identification to the level appropriate to support clinical transplant protocol.

• We revised the language now at § 493.1278(e)(1) (formerly § 493.1265(a)(1)(ii) to clarify that the techniques for crossmatching must be documented to have increased sensitivity in comparison to the basic complement-dependent microlymphocytoxicity assay.

• We revised the requirement now at § 493.1278(f)(1) (formerly at § 493.1265(b) and (c)) that requires specific testing protocols to be less prescriptive and allow laboratories to define testing policies and protocols for each type of cell, tissue, or organ to be transfused or transplanted.

• We clarified the requirement now at § 493.1278(f)(3) (formerly at § 493.1265(b)(3)) that the laboratory must have available, and follow, policies that address when HLA testing and final crossmatches are required for presensitized non-renal transplant recipients.

• We clarified the requirements now at § 493.1291(a) (formerly at § 493.1109(a)) to provide that the laboratory must have adequate systems in place to ensure test results and other patient specific data are accurately and reliably transmitted from the point of data entry (whether interfaced or entered manually) to final report destination, in a timely manner.

• We clarified the requirement at § 493.1291(c)(3) (formerly at §§ 493.1109 and 493.1109(a)) to specify that the date of the test report must be identified on the report.

• We clarified the requirement now at § 493.1291(c)(5) (formerly at § 493.1109) to indicate that the test report must include the specimen source, if applicable.

• We added language relevant to interpretation to the test report requirements now at § 493.1291(c)(6) (formerly § 493.1109(b)) for those test results that require supplemental information.

• We revised the language now at § 493.1291(j) (formerly § 493.1109(h)) by removing the words ''exact duplicate'' and clarified the language by specifying that all test reports or records of the information on the test reports must be maintained by the laboratory in a manner that permits ready identification and timely accessibility.

Subpart M—Personnel for Nonwaived Testing

• We revised the heading of subpart M to read ''Personnel for Nonwaived Testing'' to conform with the names of the new subparts J and K.

• We revised § 493.1359(a)(3) by removing the reference to ''subpart P.''

• We revised § 493.1407(e)(5) by removing the word ''assurance'' and, adding in its place, the word ''assessment.''

• We revised § 493.1443(b)(3) to allow individuals with a doctoral degree who are serving or have served as directors of laboratories performing high complexity testing before February 24,

2003, under the phase-in provision, to continue to qualify as directors of laboratories performing high complexity testing.

• We revised the requirement at § 493.1443(b)(3)(i) by removing the list of HHS-approved boards. We are placing the list in Appendix C of the State Operation Manual (CMS Pub. 7) to allow more timely updates.

• We revised § 493.1445(e)(5) to refer to the quality assessment program.

• We revised § 493.1451(c)(4) by removing the reference to § 493.1257(c) and adding, in its place § 493.1274(d) and (e).

• We revised § 493.1471(b)(2) and § 493.1485(a) by removing ''§ 493.1257(d),'' and adding, in its place, ''§ 493.1274(c).''

Removal of Subpart P

As stated in section II of this preamble (Highlights and Organization of Final Rule), we incorporated the former ''Subpart P—Quality Assurance; Moderate Complexity (Including the Subcategory) or High Complexity Testing, or Any Combination of These Tests'' under the appropriate sections now located in Subpart K, General Laboratory Systems, Preanalytic Systems, Analytic Systems, and Postanalytic Systems.

Subpart R—Enforcement Procedures

• We revised § 493.1844 by removing the reference to ''subpart P.''

Subpart T—Consultations

• We revised § 493.2001(e)(1) to read ''Criteria for categorizing nonwaived testing.''

• We revised § 493.2001(e)(4) to read ''Facility administration and quality systems standards;''

VI. Collection of Information Requirements

Under the Paperwork Reduction Act (PRA) of 1995, we are required to provide 60-day notice in the **Federal Register** and solicit public comment before a collection of information is submitted to the Office of Management and Budget (OMB) for review and approval. In order to fairly evaluate whether an information collection should be approved by OMB, section 3506(c)(2)(A) of the PRA requires that we solicit comment on the following issues:

• The need for the information collection and its usefulness in carrying out the proper functions of our agency.

• The accuracy of our estimate of the information collection burden.

• The quality, utility, and clarity of the information to be collected.

• Recommendations to minimize the information collection burden on the affected public, including automated collection techniques.

We are soliciting public comment on each of these issues for the sections that contain new information collection requirements. Except as indicated below, all of the information collection burden in this final rule has been approved by the OMB under approval number 0938–0612 through June 2004.

Because the sections in this final rule are a reorganization of former sections, the burden approval numbers cited state the best approximation we could make for which combinations of former burden numbers match with the sections as specified in this final rule. Our approximations are as follows:

Section 493.1105 Standard: Retention Requirements

Under paragraph (a)(6), Test reports, the laboratory must retain or be able to retrieve a copy of the original report (including final, preliminary, and corrected reports) at least 2 years after the date of reporting.

The change in this paragraph is that now the laboratory has the option of either retaining a copy of the report or having the capability of generating a copy of the report. This revision does not change the burden captured under OMB approval number 0938–0612.

Section 493.1241 Standard: Test Request

At paragraph (c), the laboratory must ensure that the written or electronic test requisition solicits the following:

• The sex and age or date of birth of the patient.

• The source of the specimen, as appropriate.

• The date and, if appropriate, time of specimen collection.

• Any additional information relevant and necessary to a specific test to ensure accurate and timely testing, and reporting of results, including interpretation, if applicable.

These new requirements mandate that laboratories solicit the sex and age or date of birth of the patient and, if appropriate, the source of the specimen and the time of specimen collection on the test request. In addition, the requirements clarify that the relevant information needed to ensure accurate and timely testing and reporting of results includes relevant information for interpretation of results.

We believe the burden of soliciting this information is minimal, as it is routinely captured by laboratories as part of good business practices. Therefore, while this information collection requirement is subject to the PRA, we believe the burden is exempt as defined in 5 CFR 1320.3(b)(2) because the time, effort, and financial resources necessary to comply with the requirement are incurred by persons in the normal course of their activities.

Section 493.1242 Standard: Specimen Submission, Handling, and Referral

At paragraph (a), we are clarifying the requirement, formerly at § 493.1103(a), that the laboratory's written policies and procedures for specimen labeling specify that the patient's name or unique patient identifier, and when appropriate, specimen source be on the specimen label. This revision does not add additional reporting burden for this requirement under OMB approval number 0938–0612.

Section 493.1251 Standard: Procedure Manual

Paragraph (b)(13) requires that the procedure manual include the laboratory's system for entering results in the patient record and reporting patient results including, when appropriate, the protocol for reporting ''panic or alert values.''

This requirement, formerly at § 493.1211(b)(14), now includes the provision for a written procedure describing the laboratory's processes for entering results into patient records. This revision does not change the paperwork burden captured for this requirement under OMB approval number 0938–0612.

Section 493.1253 Standard: Establishment and Verification of Performance Specifications

Each laboratory that introduces an unmodified, FDA-cleared or approved test system must, before reporting patient test results, demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the specified performance characteristics.

In addition, each laboratory that uses a test system in which performance specifications are not provided by the manufacturer, modifies an FDA-cleared or approved test system or introduces a test system not subject to FDA clearance or approval (includes standardized methods and methods developed in-house) must, before reporting patient test results, establish for each test system the performance specifications for specified performance characteristics.

Based upon the performance specifications verified or established, the laboratory must determine calibration procedures and control

procedures. Also, the laboratory must have documentation of the laboratory's performance of all activities specified in this section.

This is a 2-part requirement and will affect laboratories differently depending on whether they are verifying or establishing performance specifications for a test method. In addition, it only applies to new laboratories and new tests instituted in existing laboratories on and after April 24, 2003. Therefore, the number of laboratories needing to meet this requirement will be minimal. While this is a new requirement for some laboratories performing testing using unmodified, moderate complexity test systems approved or cleared by the FDA, it only applies to tests newly introduced into existing laboratories and to all tests in laboratories first established on or after April 24, 2003. In addition, it is common practice for test system manufacturers to perform or provide extensive assistance with this quality control activity when a laboratory buys or leases an instrument or other new test system. Thus, in practice, most of the burden for recording and documenting the quality control requirements are already born by the test system manufacturers. We do not believe that this burden will be shifted to the laboratory. Also, accrediting organizations and States with licensure programs, after which the CLIA requirements were modeled, have traditionally required laboratories to perform these activities. Therefore, while this information collection requirement is subject to the PRA, the burden is exempt as defined in 5 CFR 1320.3(b)(2) because the time, effort, and financial resources necessary to comply with the requirement are incurred by persons in the normal course of their activities.

Section 493.1256 Control Procedures

These requirements were previously at § 493.1218 and approved under OMB approval number 0938–0612. The burden associated with these requirements involves the documentation of the control results and corrective action taken when control results do not meet the laboratory's acceptability criteria. Therefore, we are revising the paperwork requirements to some extent.

Under paragraph (d), the laboratory must do the following, as applicable:

- In paragraphs (d)(3)(i) and (ii), for each quantitative and qualitative procedure, include two control materials of different concentrations and a positive and negative control material, respectively.

There may be increased reporting for unmodified moderate complexity tests (formerly at § 493.1202(c)) whose manufacturer's instructions did not include these requirements. The burden for the remainder of the tests is captured for this requirement under OMB approval number 0938–0612.

- In paragraph (d)(3)(iii), for each semiquantitative procedure, include a negative control material and, as applicable, a control material with graded or titered reactivity.

There will be an increase in paperwork burden for unmodified moderate complexity tests (formerly at § 493.1202(c)) whose manufacturer's instructions did not include this requirement and for tests not subject to the specialty requirements formerly at §§ 493.1239(b) or 493.1241(a). The burden for the remainder of these tests for this requirement is captured under OMB approval number 0938–0612.

- In paragraph (d)(3)(v), for each molecular amplification procedure, include two control materials and, if reaction inhibition is a significant source of false negative results, a control material capable of detecting inhibition.

There will be increased burden for recording the additional control results, when needed. The burden of recording the former control results is captured for this requirement under OMB approval number 0938–0612.

- In paragraph (d)(6), when a complete change of reagents is introduced, major preventive maintenance is performed, or any critical part that may influence test performance is replaced, the laboratory must, before resuming patient testing perform control material testing as specified under paragraph (d) of this section.

There will be an increase in burden for tests whose manufacturer's instructions did not include the requirements for control material testing specified under paragraph (d) of this section. The burden for the remainder of the tests is captured for this requirement under OMB approval number 0938–0612.

- Under paragraph (d)(10)(iii), when control materials providing quantitative results are used, statistical parameters for unassayed materials must be established over time by the laboratory through concurrent testing of control materials having previously determined statistical parameters.

There will be an increase in reporting for moderate complexity tests formerly subject to the phase-in at § 493.1202(c). The burden for the remainder of these tests is captured under OMB approval number 0938–0612.

In paragraph (e)(3), the laboratory must check fluorescent and immunohistochemical stains for positive and negative reactivity each time of use. Therefore, reporting will increase from one to two control results in the subspecialty of histopathology for tests performed using immunohistochemical stains. For mycobacteriology, recording control results will increase from each week of use to each time of use for fluorochrome acid-fast stains. The burden of reporting one control result is captured for these requirements under OMB approval number 0938–0612.

Under the former OMB approval, we allotted 5 minutes per day for the reporting requirements in the former § 493.1218. This time allotment was based on the assumption that most of the previously unregulated laboratories were performing moderate complexity testing and ran a total of four QC samples daily. This time allotted included reporting for the burden associated with all the specialties and subspecialties; therefore, we believe the burden was slightly underestimated.

We are allotting 5 minutes per day to perform this documentation for the specialties and subspecialties (except bacteriology, mycobacteriology, hematology, and histopathology) and are adjusting this burden to reflect the number of laboratories currently affected by this rule. We are addressing the specialties and subspecialties of bacteriology, mycobacteriology, hematology, and histopathology separately. We are assuming laboratories are documenting control activities on an average of 6 days per week. Therefore, the burden for the specialties and subspecialties (except bacteriology, mycobacteriology, hematology and histopathology) can be calculated as 5 min./day × 24 days/month = 120 min./month = 2 hrs./month 2 hrs./month × 12 months/yr. = 24 hours/laboratory/yr.

The total estimated burden for this requirement (now at § 493.1256) is 27,685 laboratories (total number of laboratories minus the number of waived laboratories, provider performed microscopy (PPM) laboratories, and previously regulated laboratories) × 24 hrs./yr. = 664,440 hrs./yr.

Section 493.1261 Standard: Bacteriology

For the subspecialty of bacteriology, in this final rule at paragraph (a), the laboratory must check the following for positive and negative reactivity using control organisms:

- Each day of use for beta-lactamase methods other than Cefinase™.
- Each week of use for Gram stains.

• When each batch (prepared in-house), lot number (commercially prepared), and shipment of antisera is prepared or opened and once every 6 months thereafter.

In paragraph (b), for antimicrobial susceptibility tests, the laboratory must check each batch of media, lot number, and shipment of antimicrobial agent(s) before, or concurrent with, initial use, using approved reference organisms and, each day tests are performed, the appropriate control organisms must be used to check the procedure.

Former Burden

In the former regulation, laboratories had to check catalase, coagulase, beta-lactamase, and oxidase reagents using a positive and negative control material each day of use. In addition, the laboratories had to check bacitracin, optochin, ONPG, XV, X, and V disks or strips using a positive and negative control material each week of use. We estimate that most bacteriology laboratories operate an average of 6 days per week; therefore, we allowed an average of 2.5 minutes per day to document the results of control testing for the reagents listed above. This resulted in the former burden, 2.5 min./day × 24 days/month = 60 min./month = 1 hr./month 1 hr./month × 12 months/year = 12 hrs./laboratory/yr.

Under the former regulation, the estimated burden for documenting control testing for the reagents above was 27,443 bacteriology laboratories × 12 hrs./yr. = 329,316 hrs./yr.

Change in Burden

In this final rule, we are allowing laboratories to check each batch, lot number and shipment of reagents (catalase, coagulase, and oxidase), disks (bacitracin, optochin, ONPG, X, V, and XV), stains, antisera, and identification systems for positive and negative reactivity, and graded reactivity if applicable. For purposes of calculating the burden, we are assuming that laboratories receive a new shipment of reagents on the average of once per month. Since the burden with documenting control testing for susceptibility tests remain the same, we are considering the burden for documenting control testing for this subspecialty to be reduced by 2.5 min./day × 23 days/month = 57.5 min./month = 0.96 hrs./month 0.96 hrs./month × 12 months/yr. = 11.5 hours/ laboratory/yr.

The total estimated reduction in burden for this requirement is 27,443 bacteriology laboratories × 11.5 hrs./yr. = 315,595 hrs./yr.

Burden in This Final Rule

The estimated burden for documenting control testing for bacteriology reagents under this final rule is 329,316 hrs./yr.—315,595 hrs./yr. = 13,721 hrs./yr.

Section 493.1262 Standard: Mycobacteriology

For the subspecialty of mycobacteriology, in this final rule at paragraph (a), each day of use, the laboratory must check all reagents or test procedures used for mycobacteria identification with at least one acid-fast organism that produces a positive reaction and with an acid-fast organism that produces a negative reaction.

Former Burden

In the former regulation, we included the requirements to document the results of control testing with the general QC procedures. However, since these documentation requirements are now under the condition, Analytic systems at § 493.1250, we have removed these documentation requirements from the general QC procedures and placed them in the subspecialty of mycobacteriology at § 493.1262.

In the former regulation, the laboratory was required, each day of use, to check all reagents or test procedures for mycobacteria identification with an acid-fast positive control organism (except the iron uptake test, which also requires a negative control). Assuming that only 35.4 percent (see section VII of this final rule, Regulatory Impact Analysis) of mycobacteriology laboratories perform identification procedures, and test an average of twice weekly, the former burden for documenting the positive control reaction for mycobacteria identification reagents and tests can be estimated as 2 min/day × 8 days/month = 16 min./month = 0.27 hrs./month × 12 months/yr. = 3.24 hrs./laboratory/yr.

The total estimated burden for documenting the positive control result is 1,127 mycobacteriology laboratories × 3.24 hrs./yr. = 3,651 hrs./yr.

As mentioned previously, the former regulation also required that the laboratory check positive and negative control materials for fluorochrome acid-fast stains each week of use and check a positive control material for other acid-fast stains each week of use. The former burden for all mycobacteriology laboratories to document these control results is estimated as 1 min/day × 4 days/month = 4 min./month × 12 months/yr. = 48 min./laboratory/yr. = 0.8 hrs./laboratory/yr.

The total estimated burden for documenting control testing for acid-fast and fluorochrome acid-fast stains is 3,185 mycobacteriology laboratories × 0.8 hrs./yr. = 2,548 hrs./yr.

The former total burden for documenting control testing for mycobacteria identification reagents and tests, and acid-fast, and fluorochrome acid-fast stains was 3,651 hrs./year + 2,548 hrs./year = 6,199 hrs/yr.

Change in Burden

Since documentation of the positive control reaction was previously required for mycobacteria identification reagents and tests and the number of laboratories performing mycobacteriology remains constant, we also estimated the increase in burden for documenting the negative control material for identification reagents and tests to be one-half the previous burden, which is ½ of 3,651 hrs./yr. (from above) = 1,826 hrs./yr.

The change in burden for increasing the frequency of acid-fast and fluorochrome acid-fast stains to daily and adding a negative acid-fast stain result is calculated as 1.5 min/day × 26 days/month = 39 min./month = 0.65 hrs./month × 12 months/yr. = 7.8 hrs./laboratory/yr.

The total increase in burden for these documentation requirements for acid-fast and fluorochrome acid-fast stains is 3,185 laboratories × 7.8 hrs./yr. = 24,843 hrs./yr.

The total increase in burden for documenting control testing for mycobacteria identification reagents and tests, acid-fast, and fluorochrome acid-fast stains is 1,826 hrs./yr. + 24,843 hrs./yr. = 26,669 hrs./yr.

Burden in This Final Rule

The total estimated burden under this final rule for documenting control testing for mycobacteria identification reagents and tests, acid-fast, and fluorochrome acid-fast stains is 6,199 hrs./yr. + 26,669 hrs./yr. = 32,868 hrs./yr.

Section 493.1263 Standard: Mycology

In the former regulation for mycology, each week of use, the laboratory was required to check all procedures for mycological identification (including germ tube test) using an organism that produces a positive reaction. Under this final rule, the requirement is eliminated. This deletion results in the QC requirements for the germ tube test to default to the general QC requirements at § 493.1256(e)(1). The general requirements specify QC testing with each new batch, lot number or shipment of reagents. Because this is a minimal decrease (we estimate the change in frequency from weekly to monthly) in burden for documenting the result of a

single control, we are unable to accurately estimate the change.

Similarly, in paragraph (a), the laboratory must check each batch, lot number and shipment of lactophenol cotton blue for intended reactivity with control organism(s). Previously, control testing of this stain was required daily. As described above, since the decrease in this burden for documenting a single control result is minor, we are unable to accurately estimate the change.

Section 493.1269 Standard: Hematology

In the former regulations for the specialty of hematology, under paragraph (b), nonmanual hematology testing systems, excluding coagulation, the laboratory was required to include two levels of control materials each 8 hours of operation. In this final rule, this requirement has been revised from every 8 hours to each day of testing under § 493.1256 and results in decreased reporting.

The revisions to this requirement result in a decrease in documenting control results since the requirement has been revised from every 8 hours to each day of testing.

Previously, we had included these reporting requirements with the general QC procedures. However, since these requirements are now under the condition, Analytic systems, at § 493.1250, we have removed these hematology requirements from the general QC procedures and placed them under Control procedures at § 493.1256.

Former Burden: Hospital and Independent Laboratories

The total number of laboratories performing hematology testing is 32,753. Of this total, 5,329 are hospitals, 3,867 are independent laboratories, 17,844 are physician's office laboratories (POLs), and 5,713 fall into a miscellaneous category of others. We assume that this burden will affect most hospitals and independent laboratories since these laboratories typically operate 24 hours per day for 30 days a month. Therefore, the burden for these laboratories is 5 min./day × 30 days/month = 150 min./month = 2.5 hrs./month 2.5 hrs./month × 12 = 30 hrs./laboratory/yr. 9,196 hospital and independent laboratories × 30 hrs./yr. = 275,880 hrs./yr.

Change in Burden: Hospital and Independent Laboratories

Since this final rule will only require controls once a day, we are allowing a ⅔ decrease in burden for these laboratories. Therefore, the decrease in burden will be ⅔ of 275,880 hrs./yr. = 183,920 hrs/yr.

In addition, the new burden for hospital and independent laboratories is 275,880 hrs/yr.—183,920 hrs./yr. = 91,960 hrs./yr.

Former Burden: POLs

For POLs that only perform hematology for 8 hours a day, there is no reduction in burden. However, many POLs have operating hours that range from 9 to 10 hours a day and these laboratories are currently required to run control materials twice a day. In estimating the burden for this category of laboratories, we are including the POLs and the ''other'' category for a total of 23,557 laboratories. In addition, we estimate that 50 percent (11,779) of these laboratories operate on a 9 or 10-hour day for 20 days a month and must run control materials twice a day. Therefore, the burden is 3.5 min./day × 20 days/month = 70 min./month = 1.2 hrs./month × 12 months/yr. = 14 hours/laboratory/yr. × 11,779 laboratories (operating on a 9 or 10 hour day) = 164,906 hrs./yr.

The remaining 50 percent of the POLs that only operate on an 8-hour day have no change in burden that is, 1.75 min./day × 20 days/month = 35 min./month = 0.6 hrs./month 0.6 hrs./month × 12 months/yr. = 7 hours/laboratory/yr. 11,779 laboratories (operating on an 8-hour day) × 7 hours/yr. = 82,453 hrs./yr.

Change in Burden: POLs

In this final rule, all laboratories will only be required to run control materials once each day. Therefore, the POLs operating on a 9 or 10-hour schedule will have their burden decreased by 50 percent. The estimated decrease in burden for this group of laboratories under this requirement is 11,779 POLs (operating on 9 or 10 hour day) × 7 hrs./yr. = 82,453 hrs./yr.

Former Burden: Total

The total estimated burden was 275,880 hrs./yr. (hospital and independent laboratories) + 164,906 hrs./yr. (POLs operating on a 9 or 10 hour day) + 82,453 hrs./yr. (POLs operating on an 8 hour day) = 523,239 hrs./yr.

Change in Burden: Total

The total estimated decrease in burden for this requirement under this final rule is 183,920 hrs./yr. (hospital and independent laboratories) + 82,453 hrs./yr. (POLs) = 266,373 hrs./yr.

Burden in This Final Rule

The total estimated burden under this final rule is 91,960 hrs./yr. (hospital and independent laboratories) + 164,906 hrs./yr. (total POLs, those operating on a 9 or 10 hour day and those operating on an 8 hour day) = 256,866 hrs./yr.

Section 493.1273 Standard: Histopathology

The revisions to this requirement result in an increase in reporting from one control slide to two control slides for each group of slides for immunohistochemical stains. Previously, we included these reporting requirements with the general QC procedures. The requirements are now under the condition Analytic systems at § 493.1250 as requirements for Histopathology at § 493.1273. Although this is an increase in reporting from one control slide to two, we cannot estimate the laboratory burden because we do not know the number of laboratories that perform immunohistochemical stains or how often the staining is performed. Additionally, many of the laboratories performing immunohistochemical stains were already testing both a positive and negative control material, and some immunohistochemical stains can be checked for a negative reaction on the same slide that contains positive reactive cells. We expect that this revision will only affect a limited number of laboratories, and the increase in burden will be small.

Section 493.1278 Standard: Histocompatibility

In the former § 493.1265(a)(13), the laboratory was required to have, at least once each month, each individual performing tests evaluate a previously tested specimen as an unknown to verify his or her ability to reproduce test results. Records of the results for each individual had to be maintained. These requirements are deleted in this final rule.

Former Burden

There is a reduction in burden for this specialty since, in this final rule, we are no longer requiring the laboratories to, at least once each month, have each individual performing tests evaluate a previously tested specimen as an unknown to verify his or her ability to reproduce test results. Therefore, we estimate that the former reporting burden for this activity to be 3 min./day for each individual, or 3 min./day × 1 month = 3 min./month × 12 months/yr. = 36 min/yr. = 0.6 hrs/individual/yr.

We estimate an average histocompatibility laboratory to employ three individuals. Therefore, the former

burden is three individuals × 0.6 hrs./yr. = 1.8 hrs/laboratory/yr.

There are 264 laboratories performing histocompatibility testing; therefore, the estimated burden for this requirement in this final rule is 264 histocompatibility laboratories × 1.8 hrs./yr. = 475 hrs./yr.

Change in Burden

Since this burden is not required in this final rule, we estimate the decrease in burden to be 475 hrs./yr.

Section 493.1291 Test Report

The following information collection requirements under paragraph (c) are new: The test report must indicate (1) either the patient's name and identification number or a unique patient identifier and identification number; (2) the test report date; and (3) the specimen source, when appropriate.

While this information collection requirement is subject to the PRA, we believe the burden with it is exempt as defined in 5 CFR 1320.3(b)(2) because the time, effort, and financial resources necessary to comply with the requirement are incurred by persons in the normal course of their activities.

If you comment on these information collection and record keeping requirements, please mail copies directly to the following:

Centers for Medicare & Medicaid Services,

Office of Strategic Operations and Regulatory Affairs, ORDI, DRD–B, Attn: Julie Brown, Room N2–14–26, 7500 Security Boulevard, Baltimore, MD 21244–1850.

Office of Information and Regulatory Affairs, Office of Management and Budget, Room 10235, New Executive Office Building, Washington, DC 20503, Attn: Brenda Aguilar, CMS Desk Officer.

VII. Regulatory Impact Analysis

Overall Impact

We have examined the impacts of this rule as required by Executive Order 12866 (September 1993, Regulatory Planning and Review), the Regulatory Flexibility Act (RFA) (September 16, 1980, Pub. L. 96–354), section 1102(b) of the Social Security Act, the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4), and Executive Order 13132.

Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety effects, distributive impacts, and equity). A regulatory impact analysis (RIA) must be prepared for major rules with economically significant effects ($100 million or more in any 1 year). This regulation has no budget implications that impact Medicare benefit payments. We have, however, performed a complete regulatory impact analysis, although the specified thresholds to require a full analysis may not have been met.

The RFA requires agencies to analyze options for regulatory relief of small businesses. For purposes of the RFA, small entities include small businesses, nonprofit organizations, and government agencies. Most hospitals and most other providers and suppliers are small entities, either by nonprofit status or by having revenues of $11.5 million or less in any 1 year. For purposes of the RFA, all laboratories are considered to be small entities. Individuals and States are not included in the definition of a small entity.

In addition, section 1102(b) of the Act requires us to prepare a regulatory impact analysis if a rule may have a significant impact on the operations of a substantial number of small rural hospitals. This analysis must conform to the provisions of section 604 of the RFA. For purposes of section 1102(b) of the Act, we define a small rural hospital as a hospital that is located outside of a Metropolitan Statistical Area and has fewer than 100 beds.

Section 202 of the Unfunded Mandates Reform Act of 1995 also requires that agencies assess anticipated costs and benefits before issuing any rule that may result in an expenditure by State, local, or tribal governments, in the aggregate, or by the private sector, of $110 million. This final rule does not mandate any requirements for State, local, or tribal governments, or by the private sector. Therefore, we certify that this rule would not have a significant economic impact on a substantial number of small entities or a significant impact on the operations of a substantial number of small rural hospitals.

Executive Order 13132 establishes certain requirements that an agency must meet when it promulgates a proposed rule (and subsequent final rule) that imposes substantial direct requirement costs on State and Local governments, preempts State law, or otherwise has Federalism implications. We have determined that this final rule does not significantly affect States' rights, roles, and responsibilities.

A. Executive Summary

This final rule includes changes that will impact many laboratories and indirectly impact manufacturers of test systems and controls. Most laboratories that perform nonwaived testing will be affected. This includes laboratories performing unmodified moderate complexity testing approved or cleared by the FDA, and laboratories testing in microbiology, syphilis serology, immunology, and hematology. Although we had insufficient data and information to calculate some of the costs and savings that may result from these changes, we estimate the overall impact will result in a savings of approximately $23 to $38 million the first year and $101 to $166 million over the next 5 years (Tables 1 and 2). The term ''savings'' as used in this RIA is defined as reduced compliance costs for laboratories subject to the CLIA regulations.

The most significant change in this final rule is related to the delayed effective dates (phase-in period) that allowed laboratories performing unmodified moderate complexity testing approved or cleared by the FDA to meet certain general QC requirements. Laboratories performing this type of testing did not have to verify methods before their introduction for patient testing or to periodically verify calibration. As shown in Table 1, we expect this change to immediately impact 29,601 Certificate of Compliance and COLA-accredited laboratories. We estimate the cost of completing the QC phase-in period to be between $28.3 million and $37.1 million the first year and between $124.1 and $162.5 million over the next 5 years.

Additional changes in this final rule will impact laboratories performing various specialties and subspecialties. The impact of these changes will vary depending on the volume and frequency of testing being done in each specialty or subspecialty.

Overall, the changes in microbiology will result in significant savings of approximately $55.9 million the first year and $245.2 million over the next 5 years. The changes in bacteriology and mycology are based on data demonstrating that for several reagents, QC is not required as frequently as required under the previous regulation. We assume the changes in bacteriology will affect 27,443 laboratories and result in immediate savings of $62.4 million and aggregate savings of $273.7 million over the next 5 years. In addition, we expect changes in mycology to affect 9,059 laboratories with immediate annual savings of $1.4 million and approximately $6.1 million savings over the next 5 years. For mycobacteriology, we are requiring more frequent QC testing and expecting this change to affect 3,185 laboratories with an estimated increase in costs of $7.9

million the first year and $34.6 million over the next 5 years.

Laboratories performing testing in syphilis serology (7,634), immunology (20,665), and hematology (32,753) can perform less frequent QC testing. We are unable to estimate the savings because we do not know how often the testing will be performed.

Finally, we are including a number of other changes that we are not considering burdensome. In many cases, we expect these other changes to have positive impacts; however, we are not able to quantify the consequences. Among these changes is the completion of the phase-in period for the laboratory director qualification requirement for high complexity testing that allowed an individual with a doctoral degree and the specified training and experience to qualify as a director of a laboratory performing high complexity testing in lieu of board certification up until December 31, 2002. To ensure a smooth transition to the new provisions for directors of high complexity testing who are not board certified (but who have doctoral degrees), we will not be holding facilities out of compliance with the provisions of the rule concerning directors who are not board certified until the effective date of this new rule, to the extent the facilities are otherwise in compliance with the requirements for laboratory directors. This means that on and after February 24, 2003, individuals with a doctoral degree who have not been grandfathered in as directors will need to be board certified to serve as directors of laboratories performing high complexity testing. The grandfather provision allows those individuals with a doctoral degree who have served or are currently serving as high complexity laboratory directors and have at least 2 years of training or experience, or both; and 2 years of experience directing or supervising high complexity testing as of December 31, 2002 to continue in this capacity without obtaining board certification. In the absence of this provision, the experienced individuals who have a doctoral degree without board certification and have served or are serving as directors of laboratories performing high complexity testing would be ineligible to continue serving as a director, resulting in costly and disruptive burdens associated with currently employed individuals obtaining board certification and laboratories replacing currently serving directors.

In summary, in the first year, we estimate the sum of all costs to be $36.2 to $45.0 million with savings of $63.8 million and a net saving of $18.8 to $27.6 million the first year. Over the next 5 years, we estimate the sum of all costs to be $158.7 to $197.3 million, a total saving of $279.8 million, and a net saving of $82.5 to $121.0 million.

In addition to overall monetary savings, this analysis acknowledges the potential for improvements in test accuracy and lower error rates in patient testing. We expect there to be improvements in the accuracy of patient testing and in accuracy of moderate complexity testing resulting from performance of method verification and calibration verification, and additional QC testing in mycobacteriology. We also expect more timely identification of potential laboratory errors resulting from the grading of more proficiency testing (PT) challenges.

TABLE 1.—IMPACTS DUE TO REGULATORY CHANGES: FIRST YEAR AND 5 YEAR TOTALS

	First year		5 Year total	
	Labs affected	Savings (costs) †	Labs affected	Savings (costs) †
Method Verification	11,248	($11.3–20.1)	29,601	($49.6–88.0)
Calibration Verification	29,601	(17.0)	29,601	(74.5)
Microbiology Changes				
Bacteriology	27,443	62.4	27,443	273.7
Mycology	9,059	1.4	9,059	6.1
Mycobacteriology	3,185	(7.9)	3,185	(34.6)
Microbiology Total		55.9		245.2
Less QC for Other Specialties				
Syphilis serology	7,634	Unknown savings	7,634	Unknown savings
Immunology	20,665	Unknown savings	20,665	Unknown savings
Hematology	32,753	Unknown savings	32,753	Unknown savings
Total		18.8–27.6		82.5–121.0

†In millions of dollars.

TABLE 2.—IMPACTS DUE TO REGULATORY CHANGES: ANNUAL IMPACTS OVER 5 YEARS

	Savings (costs)†					
	Year 1	Year 2	Year 3	Year 4	Year 5	5-Year total
Method Verification	($11.3–20.1)	($10.6–18.8)	($9.9–17.6)	($9.2–16.4)	($8.6–15.3)	($49.6–88.0)
Calibration Verification	(17.0)	(15.9)	(14.8)	(13.9)	(13.0)	(74.5)
Microbiology Changes:						
Bacteriology	62.4	58.3	54.5	50.9	47.6	273.7
Mycology	1.4	1.3	1.2	1.1	1.1	6.1
Mycobacteriology	(7.9)	(7.4)	(6.9)	(6.4)	(6.0)	(34.6)
Microbiology Total.	55.9	52.2	48.8	45.6	42.7	245.2
Less QC for Other Specialties:						
Syphilis serology	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Immunology	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown

TABLE 2.—IMPACTS DUE TO REGULATORY CHANGES: ANNUAL IMPACTS OVER 5 YEARS—Continued

	Savings (costs)†					
	Year 1	Year 2	Year 3	Year 4	Year 5	5-Year total
Hematology	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Total	18.8–27.6	17.5–25.7	16.4–24.1	15.3–22.5	14.4–21.1	82.5–121.0

† In millions of dollars.
Changes discounted at 7 percent compounded annually after Year 1.

B. Introduction

The changes in this final rule will have some impact upon nearly all laboratories performing nonwaived testing. The nature and magnitude of the specific effects on any particular laboratory will depend upon the volume and types of testing performed and the QC requirements it met under the former regulation. The most significant impact will be on laboratories performing unmodified moderate complexity testing approved or cleared by the FDA that have been following the minimal QC requirements provided during the QC phase-in period. With the completion of the phase-in, these laboratories may now be required to follow more stringent QC procedures.

QC Phase-in Requirements

Under the February 28, 1992 final rule with comment period implementing the Clinical Laboratory Improvement Amendments of 1988 (CLIA), many laboratories that had never been regulated were required for the first time to establish and perform minimum QC and quality assurance practices. Most previously unregulated laboratories were performing primarily waived or moderate complexity testing using unmodified commercial test systems. Acknowledging the burden of coming under regulation for the first time, we created a phase-in period that allowed laboratories performing unmodified moderate complexity testing approved or cleared by the FDA to perform less stringent QC procedures than laboratories performing modified moderate complexity or high complexity testing. In addition, our intent was that when the phase-in period was complete, all laboratories performing nonwaived testing would be subject to the same QC requirements. This final rule is ending the phase-in period for QC that had been extended to December 31, 2002. The QC requirements for laboratories performing unmodified moderate complexity testing are now essentially equivalent to the requirements for modified moderate complexity, and high complexity testing.

As part of the QC phase-in, the FDA was to establish a process for review and clearance of manufacturers' test system instructions for compliance with certain CLIA QC requirements. This provision would have allowed laboratories to meet the CLIA QC requirements by following the manufacturers' FDA-approved or cleared instructions. However, because the CLIA program is user fee funded, we decided it would be prudent to wait until the phase-in period ended before implementing the FDA QC review. This afforded us the survey experience necessary to determine whether an additional FDA review process beyond that already in place as part of premarket review would be of benefit to laboratories. We realized through our experience inspecting laboratories that an additional FDA review would not be of such benefit. Therefore, this prospective provision was removed in this rule.

Moderate Complexity Testing

With implementation of this final rule, laboratories performing unmodified, FDA approved or cleared moderate complexity testing must now, as applicable—

- Augment procedure manual instructions;
- Monitor laboratory environmental conditions that affect reagent storage and test system operation;
- Verify or establish performance specifications for newly introduced test systems;
- Record or document equipment maintenance and function checks;
- Perform calibration verification; and
- Follow control procedures that monitor the accuracy and precision of the testing process.

These changes will primarily impact Certificate of Compliance and COLA-accredited laboratories, because these laboratories perform the bulk of the commercial, unmodified moderate complexity testing that was subject to the QC phase-in requirements.

Moderate and High Complexity Testing

This final rule updates requirements and recognizes the improvements in technology and stability of reagents by reducing the frequency of QC testing in several specialty and subspecialty areas that include both moderate and high complexity testing. For the following specialties and subspecialties, we reduced the frequency of QC testing, relieving laboratory burden and lowering the cost per test:

- Decreased frequency of QC testing for bacteriology and mycology reagent checks.
- Decreased frequency of QC testing for general immunology and syphilis serology to daily testing from concurrent with patient testing.
- Decreased frequency for hematology QC testing to each day of use from each 8 hours of operation.

For the subspecialty of mycobacteriology, we increased the frequency of QC testing for the following:

- Added a requirement for testing negative controls to check stains and reagents.
- Increased frequency for checking fluorochrome and acid fast stains.

Laboratory Director

We are completing the phase-in qualification requirements for high complexity laboratory director that allows individuals with a doctoral degree to qualify based on training and experience in lieu of board certification until February 24, 2003. With the implementation of this final rule on February 24, 2003, board certification will be required. To ensure a smooth transition to the new provisions for directors of high complexity testing who are not board certified (but who have doctoral degrees), we will not be holding facilities out of compliance with the provisions of the rule concerning directors who are not board certified until the effective date of this new rule, to the extent the facilities are otherwise in compliance with the requirements for laboratory directors. This new final rule permits those individuals who qualified under the

phase-in provision and have served or are serving as directors of laboratories performing high complexity testing and have at least 2 years of training or experience, or both, and 2 years of experience directing or supervising high complexity testing to continue to serve as directors.

Miscellaneous Changes

There are a number of minor, miscellaneous changes. Some, like the change in the consensus requirements for PT grading from 90 percent to 80 percent, are the result of comments made to the former regulation. For the most part, these changes are considered to have no significant positive or negative impact. We consider many of them to be clarifications of implied requirements, or standard laboratory practices already in place, such as the requirement for laboratories to verify accuracy of analytes, subspecialties and specialties assigned a PT score that does not reflect the laboratories' actual test performance. In many cases, we have moved specific sections to make the regulation fit within the new regulatory framework (movement of the specimen through the laboratory) and to make the requirements easier to read and comprehend. While we expect positive benefits from these clarifications, it would be impossible to quantify these benefits.

C. Methodology and Approach

Basis for Estimates and Reliability of Projections

These projections are based upon some necessary assumptions concerning the current and future status of laboratory practices, technological advances, and the marketplace, making some degree of inaccuracy unavoidable. As each change is considered, the assumptions are stated. Due to the limitations in our data and information, we used a range of reasonable alternatives to estimate future events and reflect our degree of uncertainty. For much of this analysis, we use well-defined data from CMS Online Survey and Certification Reporting System (OSCAR) (2001) concerning laboratory demographics and test volume. When using less defined data, we made projections on the more costly side to provide an estimation of maximal impact.

We estimate the impact of these regulatory changes for those entities that these changes may affect, and we project the impact over the next 5 years. The completion of the QC phase-in period affects a portion of laboratories performing unmodified moderate complexity testing cleared by the FDA. Other changes in specialty and subspecialty QC requirements affect laboratories performing both moderate and high complexity testing. The changes in the high complexity laboratory director requirements primarily affect laboratories performing high complexity testing that need to hire a director on or after February 24, 2003. As appropriate for each specific change, in addition to the impacts on laboratories, we considered the potential impacts on manufacturers of laboratory test systems, controls, and calibration materials, and possible impacts on patients.

For this analysis, CDC used the services of Research Triangle Institute (RTI) to assist with data collection and cost-benefit analyses. RTI used data concerning current testing practices to estimate both immediate consequences and the impact over the next 5 years. A 7 percent discount rate was applied for projections after the first year, consistent with OMB recommendations (Economic Analysis of Federal Regulations under Executive Order 12866). Both RTI and HHS have sought data from a number of sources, including scientific articles, Government reports, CMS data, CDC studies, including data from CDC cooperative agreements, industry reports, reports by marketing consultants, interviews with manufacturers and laboratorians, and studies by professional groups, like the American Medical Association.

For each specific regulatory change, we outline the parties these changes will affect, methodological approach, necessary assumptions and limitations in the reliability of the conclusions, and possible alternatives.

D. Impacts

This discussion of regulatory impacts is organized as follows:

- Section 1 contains the demographics of the laboratories that the completion of the QC phase-in will impact.
- Section 2 has specific provisions not required during the phase-in period that certain laboratories will now need to meet.
- Section 3 has changes in specialty and subspecialty QC, including changes in microbiology, immunology, syphilis serology, and hematology.
- Section 4 has the completion of the phase-in requirements for laboratory directors.
- Section 5 contains miscellaneous changes, Including the change from 90 percent to 80 percent consensus requirements for PT results grading.

In this final rule impact analysis, for each regulatory change, as appropriate, our discussion is organized under the following topics:

- Rationale.
- Methodology.
- Benefits.
- Costs.
- Alternative approaches.

1. Laboratories Affected by Completion of the QC Phase-in Characteristics of Affected Laboratories Laboratory Demographics

The total number of certified and exempt laboratories in the United States (U.S.) is 174,856 (Table 5). This number includes a total of 168,688 CLIA-certified laboratories (96 percent), consisting of 91,540 laboratories with Certificates of Waiver (52 percent), 38,304 with Certificates for Provider-Performed Microscopy (PPM, 22 percent), 22,720 with Certificates of Compliance (13 percent), and 16,124 with Certificates of Accreditation (9 percent) (OSCAR, April 2001). In addition, there are 6,168 laboratories in the CLIA-exempt States of New York and Washington (4 percent).

This final rule will not affect the 74 percent of clinical laboratories holding Certificates of Waiver and PPM (129,844 laboratories). Laboratories with a Certificate of Waiver are only subject to limited CLIA requirements, they must only perform waived tests and tests cleared by the FDA for home use, follow manufacturer's instructions for testing, and maintain their waived certificates. Laboratories with a Certificate for PPM procedures must meet applicable requirements in subparts J and K of this final rule (formerly subparts J, K, and P). PPM procedures were not under the QC phase-in; therefore, PPM procedures were subject to the more stringent requirements in subpart K of the February 28, 1992 final rule with comment period. However, there are no QC materials for most PPM procedures.

For this analysis, we assume that all Certificate of Compliance laboratories perform some moderate complexity testing and that these laboratories have been meeting only the minimum QC requirements for FDA-cleared, unmodified moderate complexity test systems under the requirements of the QC phase-in period. In addition, we assume the completion of the QC phase-in would affect all of these laboratories (22,720 laboratories or 13 percent).

Similarly, we assume that the completion of the QC phase-in will affect the COLA-accredited laboratories because COLA's requirements are equivalent to the CLIA QC phase-in requirements. Therefore, these changes

will impact COLA laboratories (6,881 laboratories, 4 percent) when COLA revises its requirements to be equivalent to this final rule. Laboratories accredited by organizations other than COLA currently have QC requirements that are more stringent than those under the CLIA QC phase-in. With the adoption of the requirements in this final rule, CLIA requirements will more closely resemble these accrediting organizations' standards for QC.

Therefore, we estimate that these QC changes will immediately affect 29,601 laboratories (17 percent of the Nation's laboratories). These laboratories consist of those with a Certificate of Compliance (22,720) and COLA-accredited (6,881) laboratories. The 22,720 Certificate of Compliance laboratories that this QC change may affect consist of 1,392 Hospital (6 percent of laboratories with a Certificate of Compliance), 2,593 Independent (11 percent), 14,687 physician office laboratories (POLs) (65 percent), and 4,048 Other (18 percent) laboratories (Table 3). Since the majority of COLA laboratories are POLs (95 percent, COLA estimate), we assume all COLA laboratories are POLs for this analysis. The estimated total number of POLs that these QC changes will impact is 21,568, which comprise the largest portion of the 29,601 laboratories (73 percent) we estimated will be affected by this regulation. However, the affected POLs constitute only 22 percent of all U.S. POLs and 12 percent of all laboratories in the country. The vast majority (77 percent) of POLs hold Certificates of Waiver or PPM. In addition, changes in this final rule will not immediately affect most U.S. hospital laboratories because they are typically accredited, rather than Certificate of Compliance laboratories. The additional laboratory types in the CMS OSCAR (2001) database classified as ''Independent,'' are typically referral testing sites, and ''Other'' laboratories generally perform testing at a variety of healthcare sites including home health testing and nursing homes.

Although the percentages of laboratories with each certificate type remained relatively stable over the past several years, the absolute numbers show trends toward lower complexity certificates (waiver and PPM). For example, from 1998 to 2001, the number of laboratories with Certificates of Compliance decreased by 20 percent (5,604), and an increase occurred for both Waiver (+9 percent; 7,628) and PPM (+12 percent; 3,988) laboratories (Table 4). We expect this trend to continue in the future because of the widening availability of waived tests, many of which are considered important for on-site testing in POLs. Therefore, the long-term impact of this regulation may be mitigated by this continuing decrease in the number of Certificate of Compliance laboratories.

TABLE 3.—CERTIFICATE TYPE BY LABORATORY TYPE

Laboratory type [5]	Certificate type [1]										
	Compliance		Waiver		Accreditation		PPM		State exempt [4]		All
	N [2]	% [3]	N	%	N	%	N	%	N	%	N
Hospital	1,392	15	1,231	14	5,475	62	224	3	498	6	8,820
Independent	2,593	51	910	18	937	18	131	3	515	10	5,086
Physician Office	14,687	15	42,927	44	6,416	7	31,510	33	1,391	1	96,931
Other	4,048	7	46,472	76	3,296	5	6,439	10	3,764	2	64,019
All	22,720	13	91,540	53	16,124	10	38,304	22	6,168	2	174,856

[1] OSCAR, 2001.
[2] Number of Laboratories.
[3] Column Percent.
[4] Data from NY and WA States.
[5] Self Reported.

TABLE 4.—CHANGES IN CERTIFICATE TYPE, 1998 TO 2001

Certificate type [1]	1998		1999		2000		2001	
	N [2]	% [3]	N	%	N	%	N	%
Compliance	28,324	17	27,819	16	25,145	15	22,720	13
Waiver	83,912	52	87,754	52	89,998	52	91,540	54
Accreditation	16,469	10	17,337	10	15,885	9	16,124	10
PPM	34,316	21	36,789	22	37,535	22	38,304	22
All	163,021	100	169,700	100	171,736	100	171,010	100

[1] OSCAR, 2001.
[2] Number of Laboratories.
[3] Column Percent.

Specific Impact Dependent on Test Volume and Laboratory Type

Certificate of Compliance laboratories comprise 13 percent of U.S. laboratories and perform 991 million (19 percent) of the 5.3 billion tests annually in the U.S. (OSCAR, 2001). Our estimate of 5.3 billion tests for the year 2001 is consistent with the estimate of 5.9 billion tests for 1996 by Hoerger, Eggleston, Lindrooth and Basker (1997) and the estimate of 5.7 billion tests for the year 2000 in an Institute of Medicine report (Institute of Medicine, 2000). The average annual test volume per Certificate of Compliance laboratory is 43,618; however, the test volume distribution is skewed. Most (69 percent) Certificate of Compliance laboratories perform less than 10,000 tests per year, with 42 percent performing less than 2,000. For COLA laboratories, the average annual test volume is approximately 5,000 tests per laboratory (COLA, personal communication, June 2001), making the aggregate annual test volume for all

COLA laboratories 34 million tests. Among the Certificate of Compliance laboratories, POLs and laboratories under the classification as ''Other'' tend to have low annual test volumes, while Hospital and Independent laboratories have higher test volumes (Table 5).

This final rule will affect some aspect of these laboratories differently depending upon their annual test volume and the number of different test procedures they perform. Generally, laboratories performing a limited number of different tests will be impacted less than laboratories performing a greater number of tests. The low volume laboratories, POLs and Others, will be less impacted because they tend to have more limited test menus than those in Hospitals and Independent laboratories. However, the proportionate costs of testing are greater in low volume laboratories (Tershakovec, Brannon, Bennett, and Shannon, 1995) because of the overhead cost, including those related to CLIA.

Another major determinate of the impact of this final rule that correlates with test volume is the extent of quantitative testing performed using moderate complexity instrumentation. A CDC survey of laboratories found, for example, that among Certificate of Compliance laboratories, the use of quantitative testing instrumentation was extremely variable. Use of hematology analyzers varied from a low of 36 percent among Independent laboratories to a high of 77 percent among Hospital laboratories; for chemistry analyzers, the lowest frequency (20 percent) was among POLs, while Hospital laboratories had the highest use (83 percent) (Steindel, Rauch, Simon, and Handsfield, 2000). This survey was an unbiased on-site inventory of test systems and sampling was weighted to reflect the composition of U.S. laboratories.

We also anticipate that among Certificate of Compliance POLs, the practice size will affect the magnitude of the impact. Studies also show that practice size correlates directly with the extent of on-site testing (Ambulatory Sentinel Practitioner Network, 1996). Therefore, we expect the aggregate impact of this final rule to be less among solo practices since they perform less testing. However, solo practices have fewer employees and financial resources to execute aspects of this final rule, which may increase burden.

TABLE 5.—ANNUAL TEST VOLUMES BY LABORATORY TYPE, CERTIFICATE OF COMPLIANCE LABORATORIES ONLY, OSCAR, APRIL 2001

Laboratory type [1]	Total number of laboratories	Total number of tests [2]	Average number of tests per laboratory	Number and percent of laboratories grouped by annual test volume							
				≤2,00 tests/yr		2,000–10,000 tests/yr		10,000–25,000 tests/yr		>25,000 tests/yr	
				N [3]	% [4]	N	%	N	%	N	%
Hospital	1,392	354	254,310	444	32	56	4	148	11	744	53
Independent ...	2,593	307	118,396	572	22	481	18	433	17	1,107	43
Physician Office	14,687	147	10,008	6,899	47	4,681	32	1,617	11	1,490	10
Other	4,048	183	45,207	1,614	40	968	24	578	14	888	22
All ..	22,720	991	43,618	9,529	42	6,186	27	2,776	12	4,229	19

[1] Self-reported.
[2] In millions.
[3] Number of laboratories.
[4] Column percent.

2. Specific Changes Associated with Completion of the QC Phase-in Period

a. Procedure Manuals

Rationale

During the QC phase-in period, laboratories performing commercial, unmodified moderate complexity testing must ''have a procedure manual describing the processes for testing and reporting patient test results.'' With the completion of the phase-in, laboratories performing this type of testing will now be subject to more specific, comprehensive procedure manual requirements. Some laboratories may need to augment their current procedure manuals to meet the new requirements. Although we are unable to estimate the number of laboratories and the specific procedure manual changes they will need to make, we estimate that all Certificate of Compliance and COLA laboratories will require changes to their procedure manual.

In addition, laboratories must now document the dates of initial use and discontinuance for each procedure; and all procedures and procedural changes must be approved, signed, and dated by the current laboratory director before use.

Benefits

A comprehensive and up-to-date procedure manual is essential to ensure reliable and reproducible performance among individuals and is considered one hallmark of good laboratory practice and a necessary component of quality management.

Costs

For those Certificate of Compliance and COLA laboratories that need to amend procedure manual instructions, the cost will vary depending on the extent to which they may need to create procedural elements and the number of procedures performed in each laboratory. The cost for each laboratory will be the cost of the labor to augment documentation and the laboratory director's time in reviewing, signing, and dating procedures. We estimate that these costs will be minimal since most Certificate of Compliance and COLA laboratories do not perform a large number of test procedures and many may already have the documentation. We are unable to estimate the total cost for this requirement since we have no estimate on the extent to which procedure documentation will be necessary.

b. Test Systems, Equipment, Instruments, Reagents, Materials, and Supplies

Rationale

With the completion of the QC phase-in, laboratories performing commercial, unmodified moderate complexity testing must now meet the provisions at § 493.1252 for test systems, equipment, instruments, reagents, materials, and supplies. During the phase-in, these laboratories were required to ''follow the manufacturer's instructions for instrument or test system operation and test performance,'' which would include most of the requirements listed in § 493.1252. However, now laboratories must monitor and document conditions essential for ''proper storage of reagents and specimens, accurate and reliable test system operation and test result reporting.'' These conditions include ''water quality, temperature, humidity, and protection of equipment and instruments from electrical interruptions and fluctuations that adversely affect patient test results and test reports.''

Benefits

Monitoring and documenting environmental and other conditions necessary for proper reagent and specimen storage and test performance is essential to ensure quality test results. When conditions are outside of the prescribed acceptable range, corrective action can be taken. Without monitoring and documentation, laboratories may not be aware of conditions that may adversely affect patient test results.

Costs

The costs to implement this requirement will be minimal and will include labor to develop and maintain a monitoring and documentation system. We do not know the extent to which the specific commercial, moderate complexity procedures used in each laboratory will require monitoring of each of these conditions or the extent to which laboratories are already performing monitoring and documentation of these conditions. Therefore, we are unable to estimate a total cost for this requirement.

c. Method Verification

Rationale

Method verification is performed when a new test is brought into the laboratory and before beginning patient testing and result reporting. It consists of studies to verify that the laboratory can obtain accuracy, precision, reportable range and reference intervals with the new test system comparable to the manufacturer's specifications. During the QC phase-in period, laboratories could introduce testing using commercial, unmodified moderate complexity test systems approved or cleared by the FDA without verifying manufacturer's performance specifications (accuracy, precision, and reportable range of patient test results) before testing patient's specimens. On April 24, 2003, all laboratories must perform method verification when instituting any new moderate complexity test and before testing patient specimens, as specified in § 493.1253.

Methodology

To determine the possible impact, we did an estimate of the cost of assays to verify manufacturers' performance claims for commercial, unmodified moderate complexity tests expected to be introduced annually among the affected laboratories. For this analysis, we assumed that existing moderate complexity test systems would be retired and replaced with a new test system approximately every 5 years according to data available for a small population of laboratories. In addition, for cost calculations, we estimated the number of verification data points needed and the costs in terms of labor, materials, and reagents to perform these studies.

The cost of method verification is typically greater for quantitative tests than qualitative tests. In most cases, fewer specimens and less labor and reagents are required to verify the performance of qualitative tests. We do not know the fraction of new tests that are qualitative, so we treated all tests as if they are quantitative to calculate the maximal impact. Also, we assumed that the laboratories that this change will affect have not been performing method verification. However, we know that some manufacturers currently offer on-site verification assistance, and we expect that practice to continue; therefore, we may be overestimating the impact.

Estimates of the Incidence of New Test Introduction

Data describing how frequently new tests or test systems are introduced into laboratories were limited. For one estimate, we used the percentages of laboratories expected to add zero, one, two, three, four, or five moderate complexity tests to their test menus from a survey of laboratories participating in the Pacific Northwest Laboratory Medicine Sentinel Monitoring Network (LaBeau, Simon, and Steindel, 1999). Laboratories were asked how many nonwaived new tests they added to their test menus between April 1997 and April 1999. Although these percentages are for a 2-year time period, we conservatively assumed that all tests were adopted during the last year of the period. We assumed that the incidence of test introduction is roughly the same for the affected laboratories as for the Sentinel Monitoring Network. Multiplying these percentages by the total number of laboratories (29,601), we calculated the number of laboratories that are expected to add at least one test to their test menus in a year, approximately 11,248 (38 percent) (Table 6).

Estimate of Analyzer Replacement

Because of the small sample size, we were not confident that the survey of laboratories in the Pacific Northwest Laboratory Medicine Sentinel Monitoring Network accounted for the replacement of existing multiple analyte analyzers. Replacement of an obsolete analyzer with a new model requires verification for each analyte. Therefore, the cost of replacing analyzers depends upon the existing number of analyzers, the number of years of operation before replacement, the number of tests each analyzer performs, and the labor and reagent cost per assay for method verification. We assumed laboratories replace analyzers every 5 years and, therefore, compute the number of analyzers of each type that would require replacement each year by dividing the number of analyzers by five.

NICLTS data (Steindel, *et al* 2000) gave us the percentage of Certificate of Compliance POL, Hospital, Independent and Other laboratories having chemistry, hematology, therapeutic drug, ligand, reproductive hormone, and immunology analyzers. To determine the total number of each kind of analyzer to be replaced over the next 5 years, we multiplied these percentages by the number of Certificate of Compliance and COLA laboratories of each laboratory type to obtain the number of laboratories having each kind of analyzer, and then totaled the analyzers in each laboratory type (Table 7).

Benefits

To ensure accuracy and precision, it is especially important to demonstrate acceptable performance for a new test method before testing patient specimens. Comparing results of the new method with the manufacturer's claims and the current method, if the method is being replaced, can detect biases and problems with

reproducibility and linearity. Also, an evaluation of the appropriateness of the reference interval ensures that the test can differentiate a normal result from one suggesting a disease process. It is difficult to estimate the number of mistakes that can be averted by method verification. However, it is considered a hallmark of good laboratory practice to prevent errors when introducing a new test system, by verifying acceptable performance of the new methodology before testing patient specimens.

Costs

Number of Tests Needed To Verify Method Performance Specifications (Per Analyte)

There are no standards of practice established for method verification, and there is great variability in what laboratories currently do to verify performance specifications. The NCCLS has published several guidelines for verification of the elements of acceptable performance. One way to document performance is to use NCCLS protocols, document EP15–P for accuracy and precision, EP6–P for linearity (reportable range), and C28–A for reference intervals. The three separate protocols require a total of 120 assays, at a minimum. Reducing this number can be accomplished by performing some of the analyses together using the same specimens. Therefore, our estimate using the NCCLS protocol, in which we assumed a range of 120 to 150 assays per analyte or test, may overestimate the number of assays required.

Reagent Costs

We estimated the cost for reagents by obtaining price quotes from reagent manufacturers (Beckman-Coulter, Dade-Behring and Roche Diagnostics). Because the price estimates vary with test volumes, we assumed a moderate test volume with an average cost across analyzers to estimate an average reagent cost. We also estimated an average reagent cost to be $1.79 per test. We did not include costs for calibration or QC materials. However, many manufacturers provide assistance to laboratories for method verification, and this assistance many times includes providing reagents to the laboratory free of charge. Although manufacturers will incur some cost for reagents, the cost is significantly less than the retail sales price we quote.

Labor Estimates

Because we do not know the average number of analytes per test system, we assumed a broad range of analyst time (4 to 16 hours) at a rate of $17.90 per hour (Ward-Cook and Tannar, 2001). We are also assuming 1 hour of laboratory director time at a rate of $33.45 per hour (Bureau of Labor Statistics Occupational Outlook Handbook, 2000–2001 edition).

Materials

For the NCCLS approach, patient materials would suffice; however, these must be tested on a separate analyzer that serves as a reference for accuracy determinations. In addition, we are assuming that previously tested, stored patient samples would be used; therefore, we included locating previously tested patient materials in labor costs.

Total Costs

Based on the incidence of introduction of individual tests reported in the Pacific Northwest Laboratory Medicine Sentinel Monitoring Network survey (LaBeau, *et al* 1999), the cost of the requirement to perform method verification among affected laboratories can range from $8.3 to $15.3 million the first year (Table 6). Considering the costs of method verification for replacement analyzers, the costs can range between $3.0 and $4.8 million (Table 7). Therefore, the total first year expense for method verification may range from $11.3 to $20.1 million. The aggregate impact for method verification, with a discount over the next 5 years, may range from $49.6 to $88.0 million.

TABLE 6.—IMPACT OF METHOD VERIFICATION, NEW SINGLE TESTS

Number of tests	Percent adding	Number of laboratories adding	Number of tests added	Med tech labor cost (range)*	Lab director labor cost*	Total labor cost (range)*	Reagent cost (range)*	Total cost methods (range)
0	62	18,353	0	0	0	0	0	0
1	16	4,736	4,736	$0.34–1.36	$0.16	$0.50–$1.52	$1.02–1.27	$1.51–2.79
2	8	2,368	4,736	0.34–1.36	0.16	0.50–1.52	1.02–1.27	1.51–2.79
3	5	1,480	4,440	0.32–1.27	0.15	0.47–1.42	0.95–1.19	1.42–2.61
4	4	1,184	4,736	0.34–1.36	0.16	0.50–1.52	1.02–1.27	1.51–2.79
5	5	1,480	7,400	0.53–2.12	0.25	0.78–2.37	1.59–1.99	2.37–4.38
			26,048	1.87–7.47	0.88	2.75–8.35	5.60–6.99	8.32–15.33

*Millions of dollars

TABLE 7.—IMPACT OF METHOD VERIFICATION, ANALYZER REPLACEMENT

Analyzer type	Number of analyzers	Number of analyzers replaced each year	Medical technologist labor cost*	Laboratory director labor cost*	Total labor cost*	Reagent cost*	Total replacement cost*
TDM	3,230	646	$46.3–185.0	$21.6	$67.9–206.6	$0.45–0.56	$0.51–0.76
Chemistry	7,657	1,531	109.6–438.6	51.2	160.9–489.8	1.10–1.38	1.26–1.87
Hematology	12,439	2,488	178.1–712.5	83.2	261.3–795.7	0.27–0.34	0.53–1.13
Ligands	3,404	681	48.7–195.0	22.8	71.5–217.7	0.25–0.33	0.32–0.52
Reproduction	930	186	13.3–53.3	6.2	19.5–59.5	0.27–0.33	0.29–0.39
Immunology	223	45	3.2–12.8	1.5	4.7–14.3	0.06–0.08	0.07–0.09
			399.3–1,597.1	$186.5	585.8–1,783.7	2.18–2.72	2.98–4.77

TDM = Therapeutic drug Monitoring.
*Thousands of dollars.
*Millions of dollars.

Assumes tests per analyzer: TDM = 2, Chemistry = 15, Hematology = 1, Ligands, Reproduction & Immunology = 5

Assumes reagent cost per test: TDM = $2.88, Chemistry = $0.40, Hematology = $0.90, Ligands = $3.00, Reproduction = $2.38, Immunology = $2.38

Reliability of Estimates

The impact of method verification on any particular laboratory will depend on how many tests are introduced in any given year. The impact will be more on laboratories that are frequently expanding test menus, replacing test methods or test systems rather than those maintaining test menus and test systems. Obviously, any start-up laboratory performing nonwaived testing would be verifying the entire test menu. Nearly two-thirds of the laboratories in the Pacific Northwest Sentinel Network introduced no test systems during the 2-year interval and none introduced more than five (LaBeau, et al, 1999). Therefore, we believe while our estimates may accurately describe the impact on the universe of affected laboratories, for any particular laboratory, we may have underestimated or overestimated the consequences.

Discussions with manufacturers revealed that assistance with method verification is often included in the cost of buying or leasing an instrument or other new test system, regardless of the size of the laboratory. Regardless of whether the manufacturer assists in the verification process, the laboratory or the manufacturer or both will incur costs. What is relevant to the impact is whether the frequency of the method verification will change. Since method verification already frequently occurs in the absence of regulation and manufacturers often provide assistance, our estimate of the total cost of method verification probably overstates the incremental impact of the new requirement. However, we were unable to quantify how frequently method verification is performed currently, thereby preventing us from precisely estimating the incremental change in the frequency of method verification when this regulation becomes effective. Therefore, we may have overstated or understated the number of assays that laboratories will actually do to verify performance.

d. Calibration Verification

Rationale

During the phase-in period, laboratories performing unmodified moderate complexity testing cleared by the FDA performed testing without meeting the calibration verification requirement. On April 24, 2003, the phase-in period ends, and all laboratories must perform calibration verification at least every 6 months for each quantitative nonwaived test, as appropriate. Calibration verification is done to ensure that the test results are accurate throughout the reportable range of patient results for each test system.

Methodology

To determine the impact, we estimated the number of laboratories these changes will affect, their current menus of quantitative tests for which calibration verification would be applicable, the number of data points needed for verification and the costs in terms of labor, verification materials and reagents.

Number of Laboratories This Change Will Impact

We assumed that this QC change will affect all 29,601 laboratories, since Certificate of Compliance and COLA laboratories perform some moderate complexity testing. In addition, we assumed these laboratories have not been performing calibration verification on commercial, unmodified moderate complexity test systems.

Laboratory Menus of Tests With Verifiable Calibration

Calibration verification is performed for quantitative testing. For this analysis, we focused on multi-test clinical analyzers for which calibration verification materials are commercially available. Specifically, we estimated the fraction of laboratories that have analyzers for performing quantitative tests for chemistry, therapeutic drug monitoring, ligands, reproductive hormone testing, hematology, and immunology. By ''ligands'' we mean analytes measured by immunoassay, for example carcinoembryonic antigen, cortisol, and folate.

Number of Analytes Per Analyzer

For the purposes of estimating reagent consumption, we estimated the number of analytes being done by multi-test analyzers. We assumed that the variability of laboratory types and sizes would affect the number of different tests being performed; however, we were unable to account for the variability in this model. Because POLs comprise the largest portion of the laboratories that these changes will affect and POLs tend to have relatively limited test menus, we assumed most laboratory menus to be minimal among those laboratories that these changes will affect.

In order to estimate the number of analytes per laboratory, we analyzed data from three proficiency testing programs that target POLs (Medical Laboratory Evaluation, American Proficiency Institute, and College of American Pathologists' Excel) as a gauge of the numbers of tests offered among those laboratories these changes will affect. From these data, we estimated average test menus of fifteen chemistry analytes, two therapeutic drugs, one hematology analyte, and five for each ligand, immunology, and reproductive testing analyzer. Using this model, the specific number of analytes that must be verified has little impact on the estimates because most of the expense is in the verification kits.

Number of Data Points To Verify Calibration

At a minimum, laboratories must check three points in the reportable range to verify calibration, that is, the low, mid, and high points of the range. Although there is no requirement to perform duplicate testing at each level, it adds information about precision while adding very little to the cost of the procedure. Therefore, we included duplicate testing. We estimated that six data points are the minimum for adequate calibration verification, three concentrations in duplicate. Since calibration verification must be performed at least twice yearly, laboratories must collect a total of at least twelve data points for each analyte every year.

Benefits

We believe that calibration verification can reduce errors in patient testing by periodically providing information on the accuracy of an assay after it is calibrated, after any major maintenance or after problems are detected in routine QC. However, we are not aware of any studies demonstrating the affect of calibration verification on error rates.

Labor Costs

For estimates of labor costs, we assumed that 2 hours per year will be sufficient for each analyte for both performing the assay and inspecting the results for acceptable performance. This estimate may be too low in some instances and too high in others. The cost of the analyst time, $17.90 per hour, is the 2000 mean wage per hour for a staff medical technologist from Ward-Cook and Tannar (2001). In addition, we assumed that the labor cost of calibration verification per year is the

time we estimated it takes to perform the calibration verification (2 hours), multiplied by the analyst wage per hour ($17.90).

Cost of Verification Materials

Materials used for calibration verification span the reportable range of the method, and target values are assigned independently using accurate test methods. Acceptable materials are proficiency testing material, altered and unaltered previously tested patient specimens, primary standards or reference materials, independent calibrators, or materials for demonstrating linearity or calibration verification kits. For this analysis, we assumed laboratories will purchase calibration verification kits. However, all materials mentioned above may be used as long as the entire reportable range is tested with at least three concentrations and the nominal concentrations are independently assigned with a valid test methodology. Also, we assumed that a laboratory with any multi-test analyzer would buy a product to verify calibration of all tests the analyzer is capable of performing. We may be overestimating the cost because some laboratories do not perform all tests available on an analyzer, or we may be underestimating the cost by not including individual tests that may not be offered on a multi-test analyzer.

Our evaluation shows the costs were roughly similar for the various calibration verification products. The cost of calibration verification kits was obtained from several different suppliers of calibration verification materials (College of American Pathologists, CASCO NERL Diagnostics, Align, Sigma, R&D Systems, and Streck Laboratories). The average cost for a year's worth of calibration verification materials for comparable products was used as the cost of verification materials for each analyzer type .

Reagent Costs

We estimated the cost of reagents from price quotes by analyzer manufacturers (Beckman-Coulter, Dade-Behring, and Roche Diagnostics). This cost varies with test volume. We used the moderate volume estimate provided by these manufacturers for each analyzer type, since most of the laboratories that these changes will affect perform low to moderate test volumes. We calculated the total cost of reagents by multiplying the cost of reagents per test times the number of analytes per analyzer, the minimum number of tests per calibration verification, and the frequency of calibration verification, which we assumed to be, at a minimum, biannually.

Scope of Impact

Based upon these assumptions and estimates, we calculated the total cost of the requirement to perform calibration verification for laboratories that these changes will affect to be $17.0 million the first year, and the discounted cost will be $74.5 million by the end of the next 5 years (Table 8).

The impact to an individual laboratory will be proportional to the number of quantitative tests that need calibration verification. Larger laboratories with more analyzers and methods will need to perform calibration verification on more methods than smaller laboratories with fewer methods. Larger laboratories may also have more instrument repairs and reagent changes that may make it necessary to perform calibration verification more than twice a year. Therefore, large laboratories are more likely to incur a greater increase in the cost of calibration verification than small laboratories.

In addition, some manufacturers may furnish calibration verification materials and assist in the performance of calibration verification as part of their service. We cannot estimate the extent that this may happen; therefore, we may have overestimated the total cost.

TABLE 8.—IMPACT OF REQUIREMENT FOR CALIBRATION VERIFICATION

Test category	Laboratories affected for each test category	Labor costs per year	Cost of verification materials per year	Cost of reagents per year	Total costs per laboratory	Total costs per year †
Ther. Drug Monitoring *	3,230	$35.80	$413.00	$69.12	$517.77	$1.67
Chemistry	7,657	35.80	707.00	72.00	815.05	6.24
Hematology	12,439	35.80	575.00	10.80	621.60	7.73
Ligands	3,404	35.80	207.00	36.00	278.80	0.95
Reproductive	930	35.80	158.00	142.80	336.15	0.31
Immunology	223	35.80	150.00	142.80	328.10	0.07
Total	.....	.....	.....	.....	.....	16.98

* Therapeutic drug monitoring.
† Cost in millions.

e. Documentation of Maintenance and Function Checks

Rationale

During the QC phase-in period, laboratories performing commercial, unmodified moderate complexity testing were required to ''follow manufacturer's instructions for instrument or test system operation and test performance.'' Therefore, if the manufacturer had specific instrument maintenance procedures or function checks, the laboratories were required to perform them. With the completion of the phase-in, these laboratories must perform the maintenance and function checks according to the manufacturer, but also document their performance and results, as appropriate, and ensure that function checks are within the manufacturer's established limits before patient testing is conducted as specified in § 493.1254.

Benefits

Documentation of routine instrument maintenance and function checks provides a record for the laboratory to attest maintenance was performed according to the required schedule and to ensure that instrument function is within acceptable limits whenever patient testing is performed. This documentation is an essential element of good laboratory practice and laboratory quality management.

Costs

For those laboratories that have not been documenting maintenance and function checks, the cost to initiate this

process will depend on the labor needed to develop a documentation system. Subsequent costs will be for the labor necessary to maintain documentation, the number of instruments involved and the extent to which documentation is not currently being done. We have no data to estimate the total cost to fulfill this requirement; however, it will be of minimal impact.

f. Control Procedures

Rationale

The intent of the CLIA regulation was to impose the same requirements on all U.S. laboratories, regardless of testing site, in order to assure the public that minimum standards for quality testing were met wherever testing was performed. Under the QC phase-in requirements, laboratories performing testing using unmodified moderate complexity test systems approved or cleared by the FDA were required to test two levels of control materials each day of testing. Since many laboratories had never been regulated, they were given a phase-in period to allow them to become accustomed to meeting requirements for QC. During the phase-in, laboratories, could through the guidance in Appendix C of the State Operations Manual (SOM), use test system internal checks and controls, for example, built in procedural or electronic checks, as a substitute for one or both levels of traditional external liquid controls.

With the completion of the QC phase-in, all laboratories performing nonwaived testing are subject to the requirements specified in § 493.1256 for control procedures. The minimal number of control materials and frequency for control testing remains unchanged, two levels of control materials at least once each day of testing. We will continue to allow flexibility for laboratories to follow control procedures determined to be equivalent to testing two levels of external controls each day of testing.

We are acknowledging that laboratory technology has become simpler since the initial CLIA regulations were promulgated, and simplification and improvements are continuing. These technological advances may allow for control procedures equivalent to the traditional daily evaluation of two levels of external control materials, for example, the use of internal checks and internal controls or performance of control procedures at a frequency other than daily.

Additionally, laboratories must now meet some requirements for control use and acceptability that were not included for FDA-cleared, unmodified moderate complexity testing during the phase-in period. This includes testing controls in the same manner as patient specimens, rotating control testing among all operators who perform specific tests, and verifying the criteria for control results acceptability for quantitative tests.

Benefits

The requirements for control procedures between those in effect during the phase-in and this final rule are similar. While enforcement was permissive during the phase-in, there were no specific guidelines for laboratories to follow. With this final rule, laboratories will have guidance on what control procedures are acceptable (criteria will be specified in the SOM). In addition, the regulatory language is more specific, providing laboratories more detailed descriptions of what is required. Also, with the recognition that technology has and continues to improve, manufacturers will have more incentive to continue simplifying and improving technology to further reduce the cost of QC.

Costs

Most information on the prevalence of the reliance on internal checks and controls in lieu of using traditional external controls is anecdotal (American Association for Clinical Chemistry, 1999). A study by the Pacific Northwest Laboratory Medicine Sentinel Monitoring Network (LaBeau, et al, 1999), demonstrates that the majority of the 83 laboratories completing the survey used mechanisms other than daily testing of traditional external liquid controls for a total of 184 nonwaived tests. These control mechanisms included built-in controls, procedural controls, electronic control cartridges or devices, and control strips. Although external controls were used with 85 percent of these tests, the frequency varied. Only 15 percent used external controls daily, while the majority of the laboratories (64 percent) used external controls with each kit or lot of reagents. However, this study sample size is too small to draw general conclusions about the use of control procedures in most laboratories. Since we anticipate maintaining the status quo allowing the use of internal checks and internal controls, and the testing of external control materials at the frequency currently being performed in most laboratories for unmodified moderate complexity testing, there will be no impact on the cost.

All laboratories must now verify control results acceptability for quantitative testing. Laboratories affected by the completion of the QC phase-in might incur costs to establish this practice, since this is a new requirement. This verification is simply done through repetitive testing to ensure that the laboratory's results are within the control manufacturer's statistical parameters for the particular test system in use. We have no data on the current prevalence of this activity for those laboratories that this change may affect. For laboratories that have not been performing this verification, the costs they will incur will be for the reagents and controls for replicate testing and for the labor in testing and evaluating the statistical parameters. In many cases, replicate control testing can be done concurrent with patient testing, if the control results are within the manufacturer's stated range, reducing the cost of this requirement. Laboratories not performing this verification will use controls at an increased rate; however, they may offset this cost by the ability to use more internal or procedural QC. We have insufficient data to estimate the total costs for this requirement.

Alternative Approaches

In revising these regulations, we considered maintaining the QC phase-in requirements for QC. These phase-in requirements were intended to temporarily exempt most previously unregulated laboratories from the more stringent QC requirements such as calibration verification and method verification. Previously unregulated laboratories have had sufficient time to become familiar with regulatory requirements. Although few studies have been done linking the performance of QC procedures with patient results (Astles, et al, 1998), the standards specified in this final rule are generally considered to be basic quality requirements. Also, to maintain the phase-in requirements would create a permanent inappropriate discrepancy between what is required among the laboratories having different types of certificates and between moderate and high complexity testing. Accredited laboratories, with the exception of those accredited by COLA, and State-exempt laboratories are already required to meet more stringent QC practices than those allowed during the phase-in. We believe the completion of the QC phase-in requirements is in the best interest of the public to ensure the minimum quality laboratory standards regardless of testing site and the type of testing performed.

3. Changes in Specialty and Subspecialty QC Requirements

a. Changes to Specific Microbiology QC Rationale

We are changing the requirements for some specific QC practices in microbiology in response to public comments, including recommendations made by the American Society for Microbiology (ASM). The changes affect the subspecialties of microbiology, including bacteriology, mycobacteriology, and mycology.

In 1996, the ASM (ASM, 1996) reported to the CLIAC a study of QC failures for 304 laboratories and nearly 15,000 commercial reagent lots representing 21 different bacteriology and mycology tests. QC failure rates for the reagents studied were 0.3 percent overall. The individual failure rate for each reagent was less than 2 percent, except for X factor strips/disks, which was 2.13 percent. The results of this study prompted the ASM to propose that reagent QC be required only with each new lot for commercial microbiology reagents having a 98 percent or greater success rate. On the basis of these study results and ASM's recommendations, in this regulation, we are lowering the required frequency for reagent QC for several bacteriology tests and two mycology tests (Table 9).

For mycobacteriology, we are increasing some QC requirements based on public comments, making them equivalent with standards that already exist (Table 9). False positive results have been reported in testing for M. tuberculosis (Burman, Stone, Reeves, et al, 1997). At the same time, the incidence of infection caused by other mycobacteria requiring additional testing for accurate identification is increasing significantly. To some extent, false positive results leading to inaccurate diagnoses and unnecessary or inappropriate therapy could be reduced by including a negative reagent control with biochemical identification tests. Therefore, in this regulation, negative controls are now required in addition to positive controls each day of use for mycobacteriology reagents. In addition, positive and negative controls are now required each day of use for acid-fast stains, and each time of use for fluorochrome stains. The revised requirements are justified by the important public health consequences of accurate and timely identification of mycobacteria, including M. tuberculosis.

TABLE 9.—CHANGES TO MICROBIOLOGY QC REQUIREMENTS

Existing regulations	New regulations (specified in this rule)
Bacteriology	
Each day of use, check catalase, coagulase, beta-lactamase and oxidase reagents and DNA probes using a positive and negative control.	(NC) Each day of use, check beta-lactamase, (other than cefinase (D)) and DNA probes using a positive and negative control.
Each week of use check bacitracin, optochin, ONPG, X, and V discs or strips using a positive and negative control.	(D) Check each batch, lot number and shipment of reagents (catalase, coagulase, and oxidase), disks (bacitracin, optochin, ONPG, X, V and XV), stains, antisera and identification systems for positive and negative reactivity, and graded reactivity if applicable.
Each month of use check antisera using a positive and negative control	(D) Check each batch, lot number and shipment of antisera when prepared or opened and once every 6 months thereafter using a positive and negative control.
Mycobacteriology	
Each day of use, check iron uptake test using a positive and negative acid-fast organism and check all other reagents or test procedures using a positive acid-fast organism.	(I) Each day of use, check all mycobacteriology reagents ((NC) iron uptake test) using a positive and negative acid-fast organism.
Each week of use check acid-fast stains using positive control	(I) Each day of use, check acid fast stains using a positive and negative controls.
Each week of use, check fluorochrome acid-fast stains using positive and negative controls.	(I) Each time of use, check fluorochrome stains using positive and negative controls.
Mycology	
Each day of use, test staining materials (lactophenol cotton blue) for intended reactivity.	(D) Check each batch, lot number and shipment of lactophenol cotton blue when prepared or opened for intended reactivity.
Each week of use, check biochemical tests and mycological identification tests (germ tube) with a positive control.	(D) Check each batch, lot number and shipment of reagents, disks, stains, antisera and identification systems for positive and negative reactivity.

D = Decreased QC Testing.
I = Increased QC Testing.
NC = No change.

Methodology

The number of laboratories impacted by the QC changes for the microbiology subspecialties of bacteriology, mycobacteriology, and mycology includes laboratories issued a Certificate of Compliance or a Certificate of Accreditation performing testing in the applicable subspecialties of microbiology according to the CMS OSCAR (2001) database. The number also includes the 1,448 laboratories performing testing in bacteriology, mycobacteriology, and mycology laboratories in the exempt States.

In estimating the cost of materials for changes to the microbiology QC requirements, we used information from several different microbiology reagent manufacturers and distributors (Remel, Becton Dickinson, and Fisher), including average list prices or suggested retail prices for reagents and supplies (we acknowledge some laboratories receive lower prices through negotiated discounts or purchasing agreements). We estimated the time and amount of reagent needed to perform QC testing and maintain records for the affected tests in the applicable subspecialties, through discussions with experts in microbiology.

For the tests the QC changes will affect, the cost of QC organisms was considered negligible since organisms may be preserved and recultivated on an ongoing basis. Although the cost of maintaining cultures, including media and supplies, and the time spent in preservation and recultivation may be considerable, the changes in this final rule will not cause complete elimination of QC organism testing; therefore, the cost of culture maintenance will not

change. On the other hand, in mycobacteriology, negative control organisms are now required for biochemical identification tests. Although this could result in some initial expense if new organisms must be purchased, significant cost should not be incurred, since in some cases the same organism may be used as a control for more than one test, and some of the organisms used for negative controls may be organisms already used as positive controls for different biochemical tests.

For estimating labor costs (the larger component of the QC cost for many tests), we used the 2000 mean wage per hour for a staff medical technologist (Ward-Cook and Tannar, 2001), divided by 60 minutes per hour to calculate the cost per minute ($0.30). The cost of labor is the sum of the time required to perform QC and maintain the QC records, multiplied by the calculated wage per minute. The total cost of QC per test is the sum of the labor and material costs.

Bacteriology

We estimate that the QC changes for bacteriology will affect 27,443 laboratories, consisting of 26,610 laboratories in the CMS OSCAR (2001) database and an additional 833 bacteriology laboratories in exempt States. The changes pertain to reagents commonly used to identify bacteria. Although these reagents are primarily used for high complexity culture and identification procedures that may not be performed in a number of physician office laboratories or laboratories that perform only moderate complexity testing, we included all bacteriology laboratories in our estimates because some physician office laboratories perform high complexity culture and identification procedures, and at least one of the reagents may be used for moderate complexity tests. We realize the number of bacteriology laboratories that these QC changes affect may be overestimated.

As recommended by ASM, we are reducing QC testing to every batch, lot number, and shipment, for 10 commercial bacteriology reagents. Under the previous QC requirements for catalase, coagulase, oxidase, and beta-lactamase, QC testing was additionally required each day of use. The previous QC requirements for bacitracin, optochin, ONPG, X, V, and XV strips and disks were to test each week of use after initial testing of each batch, lot number, and shipment of reagent. For antisera (including *Salmonella* and *Shigella* antisera), we are reducing the QC testing requirements from every month of use, to every 6 months after initial QC testing.

Mycobacteriology

We expect the QC changes will affect a total of 3,185 mycobacteriology laboratories in various degrees, depending upon the services they provide. This includes 2,903 laboratories in the CMS OSCAR (2001) database and 282 laboratories in exempt States. Based on estimates of the levels of mycobacteriology testing performed in the U.S. (CDC, 1995), all mycobacteriology laboratories perform acid-fast stains and could be impacted by the changes to the QC requirements for this testing. However, according to the estimates above, only 35.4 percent (1,127) of mycobacteriology laboratories perform mycobacterial organism identification, including 24.4 percent that perform acid-fast stains, primary culture, and identification (at least of *M. tuberculosis* complex), and 11.0 percent that perform acid-fast stains, primary culture, identification, and drug-susceptibility testing. Therefore, this number represents the maximum number of laboratories that could be fully impacted by all QC changes for this subspecialty.

For acid-fast stains, we are now requiring positive and negative control organisms to be QC tested each day of use rather than each week of use. In addition, we are now requiring that fluorochrome acid-fast stains be QC tested each time of use rather than each week of use. Although not all mycobacteriology laboratories perform both types of stains on a daily basis, the specific percentage of laboratories performing each type of stain is unavailable. We conservatively estimated that the QC change will affect all mycobacteriology laboratories for both staining procedures and will require the laboratories to perform QC testing for each procedure at least daily. However, professional standards of practice recommend QC for acid-fast stains each time of use, and the QC changes will not impact laboratories following these guidelines.

For conventional biochemical reagents and test procedures for mycobacterial identification from culture, we are now requiring that a negative control organism be tested in addition to a positive control organism each day of use. Based on the biochemical tests used for mycobacterial identification as listed in *Essential Procedures for Clinical Microbiology* (Eisenburg, 1998), we estimate 10 additional negative controls for biochemical tests may be performed by each laboratory depending on the organism to be identified. However, our estimates of the additional QC required and number of laboratories that these changes will impact could be inflated for several reasons. First, many mycobacteriology laboratories now use molecular methods for organism identification in lieu of conventional biochemical tests (we are not changing the QC requirements for molecular methods). According to an ASM survey presented to the CLIAC in 1999, 78 percent of the responding laboratories performing mycobacterial identification used molecular methods. It is likely that this percentage will increase in the future as new technology continues to be developed. Second, a significant number of mycobacteriology laboratories only identify *M. tuberculosis* and do not use biochemical tests to identify additional species of mycobacteria. Last, professional standards and at least one accreditation organization already recommend or require a negative control in addition to a positive control for each identification test; therefore, the increase in the requirement will not impact laboratories already meeting these standards. Since sufficient data are not available to quantify these considerations, we estimate a maximum of 35.4 percent of mycobacteriology laboratories will have to perform additional QC for conventional biochemical tests.

Mycology

We are reducing the QC testing for the germ tube test by eliminating the positive control each week of use after initial testing of positive and negative controls with every batch, lot number, and shipment. We are also reducing the QC testing for lactophenol cotton blue from checking this stain for intended reactivity each day of use, to requiring QC testing only with each batch, lot number, and shipment. We do not expect the QC changes to affect all 18,117 laboratories performing mycology testing (17,784 mycology laboratories in the CMS OSCAR (2001) database and 333 mycology laboratories in exempt States), since the impact of decreasing the QC testing will differ among laboratories depending on the testing performed and the numbers of positive cultures obtained by these laboratories. For both the germ tube test and the lactophenol cotton blue stain, we conservatively estimate that the reduction in QC testing will affect 50 percent of the total laboratories (9,059), those being hospital and independent laboratories that would perform the high complexity culture procedures that require the use of these reagents.

Benefits

Bacteriology

Reducing the QC testing requirements for bacteriology results in a significant decrease in costs for the laboratory, including savings in reagents, supplies, and labor. To estimate the impact of these reductions, the QC cost associated with the changes must be compared to the current cost of QC testing. We assumed laboratories are currently performing QC testing for each batch, lot number, and shipment of reagents; therefore, this practice is not affected by these QC changes. For catalase, coagulase, oxidase, and beta-lactamase, eliminating the daily QC requirement results in a savings for each of these tests equivalent to the cost of the daily QC. Similarly, by eliminating the weekly QC requirement for bacitracin, optochin, ONPG, X, V, and XV strips and disks, there is a savings for each of these tests equivalent to the cost of the weekly QC. For antisera (for example, *Salmonella, Shigella* typing sera), we are reducing QC testing from every month of use to testing once every 6 months after the initial QC testing of each batch, lot number, and shipment of reagent. Assuming an average shelf life of 2 years before expiration results in cost saving of 20 QC tests.

In addition to the direct financial savings in bacteriology laboratories, reducing the QC testing will also result in a time savings equal to the time previously required to perform the testing and maintain QC records on a daily, weekly, or monthly basis. This time saving could lead to increased productivity in bacteriology laboratories.

To calculate the savings by reducing requirements for QC testing in bacteriology, we estimated the baseline expenses per laboratory for performing each QC test. In calculations for beta-lactamase testing, as per the ASM study, we assume laboratories use Cefinase™ as their method of testing. After estimating the cost per individual QC test (positive and negative controls), we then determined the change in cost per day, week, and year (Table 10). In determining these changes, we considered the decrease in frequency of testing for each reagent (previously daily vs. weekly vs. monthly). To calculate weekly changes, we used an average of 6 days per week for laboratory operations, recognizing that while most hospital laboratories operate 7 days a week, physician office laboratories (that perform some culture and identification procedures) may only operate 5 days a week. Since we estimate all bacteriology laboratories use all tests for which QC is reduced, to determine the total annual savings per laboratory, we added the QC savings for each individual test.

To estimate the total annual savings in QC costs for all bacteriology laboratories, we multiplied the total annual savings per laboratory by the number of laboratories affected (27,443), and estimated a total cost savings of $62.4 million the first year.

TABLE 10.—CHANGE IN COST PER TEST FOR REVISED BACTERIOLOGY QC REQUIREMENTS

Reagent	Labor cost*	Reagent amount	Reagent cost	Total cost per test	Change in cost per day	Change in cost per week	Change in cost per year
Catalase	$0.60	1 drop	$0.08	$0.68	−$0.68	−$4.08	−$212.16
Coagulase	0.60	2 drops	0.17	0.77	−0.77	−4.62	−240.24
Oxidase	0.60	1 drop	0.06	0.66	−0.66	−3.96	−205.92
Cefinase	0.60	2 discs	2.65	3.25	−3.25	−19.50	−1,014.00
Bacitracin	0.60	2 discs	0.40	1.00	−0.17	−1.00	−52.00
Optochin	0.60	2 discs	0.33	0.93	−0.16	−0.93	−48.36
ONPG	0.60	2 discs	0.98	1.58	−0.26	−1.58	−82.16
X	0.60	2 strips	1.60	2.20	−0.37	−2.20	−114.40
V	0.60	2 strips	1.60	2.20	−0.37	−2.20	−114.40
XV	0.60	2 strips	1.60	2.20	−0.37	−2.20	−114.40
Antisera	0.60	2 drops	6.98	7.58	−0.24	−1.46	−75.80
Total							−2,273.84

*Labor cost estimate for each reagent includes one minute to perform QC test and one minute for recording and monitoring QC results.

Mycobacteriology

Erroneous test results can lead to inaccurate diagnoses and unnecessary or inappropriate therapy. When this pertains to *M. tuberculosis* or other mycobacteria currently emerging as significant pathogens, it could have substantial cost implications or adverse health outcomes due to the side effects of drugs used to treat infections caused by these organisms. Therefore, it is critical for laboratories to rapidly detect mycobacteria and accurately identify individual species within this genus. For laboratories performing acid-fast and/or fluorochrome acid-fast stains, accuracy is best ensured by including positive and negative controls each day (acid-fast) and each time (fluorochrome acid-fast) of use. For laboratories using conventional biochemical tests to identify mycobacteria, erroneous test results can most likely be prevented by including a positive and negative control organism for each test each day of use. Although difficult to quantify, the increased costs for additional QC testing are outweighed by the benefits of prompt, accurate mycobacterial detection and identification, and appropriate therapy for mycobacterial infections.

Mycology

Reducing the QC testing requirements for the germ tube test and lactophenol cotton blue stain will result in a cost and time savings for mycology laboratories. Since weekly QC is eliminated for the germ tube test, the financial savings will equal the cost of weekly QC, and the time savings will equal the time spent on a weekly basis performing and recording QC for this test. For lactophenol cotton blue, required QC testing each day of use is now eliminated. The cost and time savings resulting from this reduction is based on calculations assuming this test is performed an average of twice a week, when positive fungal cultures are detected.

We estimated the savings for QC testing in mycology by determining baseline expenses for each germ tube test labor ($0.90) and materials ($0.73), and each lactophenol cotton blue test labor ($0.60) and materials ($0.06), followed by calculation of the weekly and annual savings that will be realized

by reducing the QC frequency for these tests. Since we estimate that these changes will affect 50 percent of mycology laboratories, the total annual cost savings in mycology will be the annual savings per laboratory multiplied by half the number of mycology laboratories (9,059), an estimated total cost savings of $1.4 million the first year.

Costs

Mycobacteriology

We estimated the cost for the changes to mycobacteriology QC testing in the same manner as we estimated savings for bacteriology (Table 11). However, in mycobacteriology, not all laboratories will be affected for every test, since no more than 35.4 percent of laboratories perform organism identification. Therefore, when estimating the overall costs of increasing the mycobacteriology QC requirements, we considered the difference in the number of affected laboratories in the calculations.

When calculating costs for the acid-fast and fluorochrome acid-fast stains, we estimated that for each test, mycobacteriology laboratories would test two QC slides on at least a daily basis. Although QC is required each time of use for fluorochrome acid-fast stains (which can differ from each day of use), we assume QC would be performed daily and that each laboratory performs both acid-fast and fluorochrome acid-fast stains daily and will incur an increase in QC testing costs for both methods. However, some mycobacteriology laboratories use only one method of staining, and some laboratories already check QC slides each time of use. The percentage of laboratories using each type of stain exclusively or already performing QC each time of use is not available. Therefore, our estimate of the cost impact of this increase in QC testing is higher than the actual costs that will be incurred. When calculating the weekly QC testing costs for acid-fast stains, we used 7 days for laboratory operations, taking into account the CDC recommended turnaround time of 24 hours (Huebner, Good and Tokars, 1993) for reporting acid-fast smears.

TABLE 11.—CHANGE IN COST PER TEST FOR REVISED MYCOBACTERIOLOGY QC REQUIREMENTS

	Labor cost	Reagent amount	Reagent cost	Total cost per test	Change in cost per day	Change in cost per week	Change in cost per year
Identification Tests[1]	[2] $6.00	Variable	$20.46	$26.46	+$7.56	+$52.92	+$2,751.84
Acid-fast Stains	[3] 1.80	2–3 mL of 3 solutions	0.61	2.41	+2.41	+14.46	+751.92
Fluorochrome Stains	[3] 1.80	2–3 mL of 3 solutions	0.60	2.40	+2.40	+14.40	+748.80
Total							+4,252.56

[1] Estimate includes the following tests: arylsulfatase, 68 degree catalase, semi-quantitative catalase, NaCl tolerance, niacin, nitrate, pyrazinamidase, tellurite reduction, Tween 80 hydrolysis, and urease.
[2] Combined labor cost estimate for each reagent/test includes one minute to perform QC test and one minute for recording and monitoring QC results.
[3] Labor cost estimate for each stain procedure includes five minutes to perform QC test and one minute for recording and monitoring QC results.

For conventional biochemical reagents and identification procedures used on mycobacterial culture isolates, we calculated the potential cost increase for adding a negative control to each test based on 10 biochemical reagents (or tests) used for mycobacterial identification, as listed in Essential Procedures for Clinical Microbiology (Eisenburg, 1998). Although several additional biochemical tests can be used in the conventional scheme of mycobacterial identification, most of these tests were not included in our calculations since they are growth tests on certain selective media, which would not be subject to increased QC requirements. The iron-uptake test was also not included in our calculations since a negative control was previously required for this test. In estimating the change in cost for these identification procedures, the cost of labor for these tests was first calculated for a single test and then multiplied by 10. We assume the same approximate time is required to perform and record each QC test. The total reagent cost was determined by adding the cost of reagents for each individual test. The total cost for all 10 tests is the sum of the labor and reagent costs. Since in most laboratories these tests are performed less frequently than acid-fast stains or bacteriology identification tests, our estimates assume that each of these tests would be run twice per week. The additional cost for each laboratory per week is equal to twice the total cost for all 10 tests, and the additional annual cost per laboratory is estimated on the basis of this total weekly cost.

To estimate the total annual increase in the cost of QC for mycobacteriology, we multiplied the increased costs for acid-fast and fluorochrome stains by the total 3,185 mycobacteriology laboratories, and multiplied the increased costs for conventional biochemical identification tests by 35.4 percent of the total number of laboratories (1,127), and then added these amounts. We estimated the total cost increase would be $7.9 million the first year.

Error Rates

Bacteriology

We do not expect increased error rates in patient testing for the QC changes in bacteriology. As reported in the ASM study, the QC failure rates for laboratories participating in the study translated into one failure for all reagents surveyed every 53 years (ASM, 1996). Since in many cases, a single reagent or test is only a part of a bacterial identification scheme, these rare failures are not likely to lead to errors in organism identification or patient testing.

Mycology

We expect no additional errors as a result of the decreased requirements for QC in mycology.

Scope of Impact

The changes in QC requirements for microbiology laboratories will result in significant cost savings overall, on an annual and 5-year basis, when considering the net effect of the changes being implemented in the subspecialties of bacteriology, mycobacteriology, and mycology. The decreased QC requirements in bacteriology and mycology are expected to impact all U.S. laboratories performing this testing under a Certificate of Compliance, Certificate of Accreditation, or State exemption. We estimate the total cost savings for each microbiology laboratory

performing bacteriology testing to be $2,274 the first year. By multiplying this number by the total number of bacteriology laboratories (27,443), we estimate the total savings for bacteriology laboratories to be $62.4 million the first year and the overall savings over the next 5 years to be approximately $273.7 million for bacteriology.

For mycology, we estimate the total cost savings the first year per laboratory will be $153, and the change will affect 9,059 mycology laboratories with total savings of $1.4 million. We estimate overall savings will be $6.1 million for the next 5 years.

Although the increase in QC requirements for mycobacteriology will result in increased costs for microbiology laboratories conducting this testing, the impact will not affect all laboratories to the same extent, as previously explained. In fact, laboratories previously following professional standards of practice for mycobacteriology will not be impacted at all by these QC changes. Mycobacteriology laboratories will likely incur increased QC costs for acid-fast and/or fluorochrome stains, an estimated maximum increase of $1,501 per laboratory the first year, and $4.8 million overall, assuming laboratories use both methods of staining, and did not previously test controls each time of use. Since only 35.4 percent of mycobacteriology laboratories perform organism identification, the impact of increasing the QC requirements for certain identification tests will affect significantly fewer laboratories. We calculated this increase to cost $2,752 per laboratory the first year, with a maximum cost of $3.1 million overall. However, as explained previously in the Mycobacteriology subsection of the Methodology section, we believe this cost impact is overestimated for the increased QC for biochemical identification tests. Evidence shows that with newer technology, fewer laboratories use the older conventional tests, and this is expected to further decrease as technology continues to improve. In addition, laboratories offering limited services may not use as many biochemical identification tests if they only identify a limited number of organisms. Last, since professional standards and an accreditation organization already recommend or require negative control organisms, many laboratories may already be including the controls we are now requiring in this regulation. Therefore, the combined annual estimate of increased QC costs for mycobacteriology laboratories of $7.9 million overall and the next 5 year estimate of $34.6 million are likely inflated to some degree.

To summarize, the total savings in QC testing costs that will result from the changes in the microbiology requirements is the sum of the savings in the subspecialties of bacteriology and mycology, minus the cost increases in the subspecialty of mycobacteriology, a minimum total cost savings for microbiology laboratories of $55.9 million the first year. The savings projected over the next 5 years are approximately $245.2 million.

Alternative Approaches

For bacteriology and mycology, one alternative approach would be to continue to require QC testing for all reagents at the same frequencies as specified in the February 1992 regulations. However, there are no data that support continuing these frequencies to ensure the quality of patient testing. We believe if the previous frequencies were maintained, the total financial costs in labor and materials would far exceed the possible benefits in detecting problems with reagents. Another approach we considered is QC testing less frequently than with every batch, lot number and shipment of reagents (catalase, coagulase, beta-lactamase, oxidase, and germ tube test), disks and strips (bacitracin, optochin, ONPG, X, V, and XV), stains (lactophenol cotton blue), and antisera. However, because damage or improper handling of each batch, lot, or shipment can result in compromised reagent integrity, we did not consider this to be acceptable. We also considered leaving the requirement for monthly testing of antisera in place, but since there are no data to support this frequency, and the ASM data showed the reagents are relatively stable, we considered QC testing every 6 months adequate for these relatively expensive reagents with extended shelf lives.

For mycobacteriology, we considered not requiring a negative control with daily use of identification reagents, and not requiring QC daily for acid-fast stains, and each time of use for fluorochrome stains. However, the expense of increasing these requirements is relatively small because so few laboratories are impacted and in practice the incremental impact of adding a second control is relatively small. We cannot quantify the impact on error rates of not implementing these changes, but false positive tests in mycobacteriology can result in considerable extra expense in patient care.

b. Changes in Required QC Frequency for Syphilis Serology, Immunology, and Hematology

Syphilis Serology

We estimated that the reduction in frequency for syphilis serology QC testing may affect 7,634 laboratories (Certificate of Compliance (3,068), Certificate of Accreditation (4,070), and State-exempt (496)) (OSCAR, 2001 and the States of New York and Washington). Laboratories will be required to run controls each day patient specimens are tested, rather than each time they are tested. For laboratories testing patient specimens more than once a day, this change will result in a cost savings. However, we cannot estimate the amount of savings, because we do not know how many of these laboratories conduct testing more than once per day.

Immunology

There are a total of 20,665 laboratories (Certificate of Compliance (9,728), Certificate of Accreditation (10,285), and State-exempt (652)) performing immunology testing that may be affected by the reduction in the frequency for immunology QC testing. Under this final rule, laboratories must perform control procedures each day of testing, rather than concurrent with each testing event. We do not know how many of these laboratories test patient specimens more than once per day for each immunology procedure; therefore, we cannot estimate the cost savings if control procedures are performed less frequently. However, these provisions for the frequency of control testing do not supercede manufacturers' instructions or laboratory specifications that may require control testing more frequently; for example, each time patient specimens are tested.

Hematology

For hematology, we are reducing the required frequency for control testing from once each 8 hours of operation to once each day of testing. There are a total of 32,753 laboratories (Certificate of Compliance (16,332), Certificate of Accreditation (15,477), and State-exempt (944)) that perform hematology testing to which this change may apply. We do not know the exact number of laboratories that this change will affect because this change will only impact laboratories performing testing longer than 8 hours per day. However, we expect it will affect most hospital laboratories and many independent laboratories, since the majority of hospitals and independent laboratories operate 24 hours per day. For these

laboratories, if manufacturer instructions and laboratory specifications allow, performance of two control testing events per day can be eliminated for each hematology analyzer. Therefore, the aggregate savings may be significant, but we cannot estimate the impact.

Alternative Approaches

For these three changes, the aggregate impact will be a cost savings; however, we have insufficient information to estimate the reduced burden or savings in reduced analyst time, cost of reagents, and control materials associated with the reduced frequency of control material testing. We considered leaving the requirements for control procedures unchanged; however, based upon the current stability of the test systems used in these three areas, we have determined that few additional testing errors would be prevented by more frequent control testing.

4. Completion of Laboratory Director Phase-in

We are completing the phase-in qualification requirement for high complexity laboratory director that allows individuals with a doctoral degree to qualify based on training and experience in lieu of board certification. With the implementation of this final rule, board certification will be required under one provision. However, under the second provision, we are allowing individuals, who qualified under the phase-in provision and who have served or are now serving as directors of laboratories performing high complexity testing and have at least 2 years of training or experience, or both, and 2 years of experience directing or supervising high complexity testing to continue to serve as laboratory directors. To ensure a smooth transition to the new provisions for directors of high complexity testing who are not board certified (but who have doctoral degrees), we will not be holding facilities out of compliance with the provisions of the rule concerning directors who are not board certified until the effective date of this new rule, to the extent the facilities are otherwise in compliance with the requirements for laboratory directors.

Rationale

Personnel qualifications are considered an essential benchmark of performance and requiring appropriate qualifications for the complexity level of testing performed by the laboratory is in the best interest of quality testing. High complexity testing requires more extensive knowledge, training, and experience to perform the management and administrative duties necessary to ensure that personnel are competent, methodologies are appropriate, and the quality control and quality assessment programs are suitable for the testing performed. The high complexity laboratory director qualification requirements in this final rule balance the quality concerns with the need to ensure continued access to high complexity testing.

Methodology

To determine the impact of these laboratory director qualification requirements over time on laboratories performing high complexity testing, we estimated the number of high complexity laboratories potentially impacted and the number of qualified individuals available to serve as high complexity laboratory directors during the next 5 years.

Laboratory Demographics

Using the CMS OSCAR (2001) database, we have determined that approximately 8,000 of the 22,720 Certificate of Compliance (COC) laboratories (35 percent, or 4.7 percent of all CLIA laboratories) perform some high complexity testing. To determine the total number of Certificate of Accreditation (COA) laboratories that perform high complexity testing, we included the approximately 9,200 laboratories accredited by five of the CLIA-approved accreditation organizations (American Association of Blood Banks, American Osteopathic Association, American Society for Histocompatibility and Immunogenetics, College of American Pathologists, and Joint Commission on Accreditation of Healthcare Organizations). The majority of these laboratories are independent or hospital-based and are assumed to perform some high complexity testing. We also estimated that approximately 1,700 of the 6,881 COLA-accredited laboratories (25 percent) perform some high complexity testing. In addition, the number of high complexity laboratories in the two CLIA-exempt States, New York (540) and Washington (235), is approximately 775 laboratories (New York and Washington, personal communication, March 2002). Therefore, the total number of CLIA laboratories (including New York and Washington) performing some high complexity testing in the United States is estimated to be approximately 19,700 laboratories.

As previously mentioned and illustrated at Table 4, the percentages of laboratories with each certificate type have remained stable over the past several years; however, the absolute numbers show trends toward lower complexity levels (waiver and PPM). While we expect this trend to continue in the future because of the widening availability of waived tests, we assume that COC laboratories switching to waiver and PPM certificates are those that perform only moderate complexity testing and the number of COC laboratories performing some high complexity testing will remain stable. In addition, we assume the number of accredited laboratories performing some high complexity testing will remain fairly stable, as has been the trend in the past several years.

High Complexity Laboratory Director Demographics

We also used the OSCAR (2001) database to identify the CLIA qualification requirements by which those individuals currently serving as laboratory directors of COC high complexity laboratories qualified. Using this data, we have calculated that 28 percent of these laboratories are directed by board-certified pathologists; 56 percent by licensed physicians with laboratory training or experience; 5 percent by individuals with doctoral degrees; 3 percent by individuals who have been serving as laboratory directors and were qualified as a laboratory director on or before February 28, 1992 (according to the March 14, 1990 final rule with comment period (55 FR 9538) published in the **Federal Register**); 7 percent by individuals who on or before February 28, 1992 were qualified under State law to direct a laboratory in the State in which the laboratory was located; and less than 1 percent by individuals who meet the qualifications currently at § 493.1443(b)(6) for the subspecialty of oral pathology.

We assume individuals currently serving as high complexity laboratory directors will retire at approximately the same rate as projected for the general population; that is, on average 3.8 percent per year for fiscal years 2001 through 2005 (U.S. Office of Personnel Management, Central Personnel Data Files, 2000). Therefore, we anticipate 3.8 percent of the approximately 19,700 high complexity laboratories (750) will need to hire a new laboratory director each year for the next 5 years. Pool of Individuals Qualified to Serve as High Complexity Laboratory Directors.

Using data (September 2000) from the American Board of Medical Specialties (ABMS), we estimated the total number of physicians that have 1 year of

laboratory training during medical residency to be 17,400. In addition, ABMS reports 5,784 pathologists received board certification over the past 10 years. This number is consistent with the Accreditation Council for Graduate Medical Education's (ACGME) data indicating there are approximately 2,660 anatomical and clinical pathology residents enrolled through the current academic year (ending June 2002). These residents will be eligible for board certification over the next 4 years.

The total number of board-certified doctoral-degreed individuals is estimated to be 2,090 (American Board of Bioanalysis (ABB), American Board of Clinical Chemistry (ABCC), American Board of Forensic Toxicology (ABFT), American Board of Medical Genetics (ABMG), American Board of Medical Laboratory Immunology (ABMLI), American Board of Medical Microbiology (ABMM), and National Registry of Certified Chemists (NRCC)). In addition, one HHS-approved board reports an average of 8 individuals receiving certification annually, another board reports an average of 11 annually, and a third board reports 37 annually (AAB, ABCC, ABFT, ABMLI, ABMM, NRCC, personal communication, March 2002).

Based on the data provided by the HHS-approved boards, ABMS, and ACGME, we believe there will be a sufficient number of individuals available to fill the possible 750 high complexity laboratory director vacancies per year over the next 5 years. Moreover, only 5 percent of the COC high complexity laboratories currently employ a laboratory director with a doctoral degree. We believe the percentage of COA and Washington State high complexity laboratories employing a laboratory director with a doctoral degree may be about the same or lower. Therefore, we estimate that approximately 180 of the 958 COC, COA, and Washington State high complexity laboratories that employ a doctoral-degreed individual as a laboratory director may have to replace their director during the next 5 years (36 annually). We did not include the high complexity laboratories in New York because they require laboratory directors to have ''specific'' training or experience in the specialty(ies) of testing the laboratory performs.

Benefits

Impact

There will be no immediate impact because the second provision included in this final rule allows individuals who have served or are currently serving as laboratory directors and have at least 2 years of training or experience, or both, and 2 years of experience directing or supervising high complexity testing to continue in their capacity without obtaining board certification. This provision circumvents the costly and disruptive burdens associated with currently employed individuals obtaining board certification and laboratories, which perform high complexity testing, replacing currently serving directors.

With regard to future impact, available data indicate there are ample numbers of qualified individuals available to fill the estimated annual high complexity laboratory director vacancies over the next 5 years. In addition, the CLIA regulations permit qualified individuals to direct up to five laboratories, which may further lessen the burden associated with replacing retiring laboratory directors. However, States and accrediting organizations may have more stringent qualification requirements for laboratory directors and affected laboratories would need to continue to meet these requirements.

Costs

The provisions in this final rule at § 493.1443(b)(3), will have no immediate costs, and we believe the costs over the next 5 years will be no greater than the costs laboratories performing high complexity testing currently experience when replacing directors.

Alternative Approaches

In the December 28, 2001 proposed rule, we considered qualifying individuals with a doctoral degree and 6 years of laboratory training and experience, or both (including 2 years experience directing or supervising high complexity testing), as directors of laboratories performing high complexity testing. While we offered this as an alternative qualification pathway, we agree with the majority of commenters and the CLIAC recommendation that the provision is not commensurate with the responsibilities of a high complexity laboratory director or consistent with the qualification requirements and responsibilities specified for the other CLIA laboratory personnel categories. Moreover, we have determined that this qualification pathway is not needed to ensure a sufficient pool of qualified individuals to serve as high complexity laboratory directors and thus continued access to high complexity testing.

5. Miscellaneous Changes

The reorganization of this final rule reflects the flow of laboratory testing (from receipt of the specimen through test performance, test reporting and systems' assessments), eliminates duplicative requirements, and rewords certain requirements. In response to comments received to previous rulemakings, wherever possible we have made changes to the regulations to reduce the burden and expense to laboratories. Also, in recognition of new and emerging technologies and methodologies, obsolete requirements have been deleted and a few new requirements have been added. Listed below are several of these revisions, not yet discussed in this impact analysis, which may result in some change in costs or burden for laboratories. While we believe the change in costs or burden, or both, will be relatively minor, lack of data and information makes these estimates either difficult or impossible to quantify.

Revisions Resulting in No Change in Burden and Costs

The FDA QC review process was intended to be implemented when the QC phase-in ended, but we established through our survey process that the review would be not be of benefit to laboratories. Because this review was not implemented, there is no impact.

- Records of test system performance specifications established or verified as required under § 493.1253 must be retained for the period of time the test system is in use. Because this information provides important data about the laboratory's test system performance (for example, accuracy, precision, and reportable range of patient results) that the laboratory is required (formerly at § 493.1109(g), now at § 493.1291(e)) to provide to clients upon request, laboratories should have already been maintaining this information. Therefore, there is no additional burden with this change.
- When a laboratory transcribes or enters test requisition or authorization information into a record or information system, it must ensure that the information is transcribed or entered accurately. Formerly at § 493.1701, laboratories were responsible for identifying and correcting problems and ensuring accurate, reliable, and prompt reporting of test results. Inaccurate transcription of test requisition or authorization information would be one example of a problem, if left uncorrected, that could interfere with both the reporting of test results and the accuracy of the results. For this reason, we believe this new requirement should have no impact on the laboratory's burden or costs.

• Section 493.1254 now specifies that when using unmodified manufacturer's equipment, instrument or test systems, the laboratory must follow the manufacturer's instructions for maintenance and function check protocols rather than establish its own. While this revision results in a less stringent requirement than that specified under former § 493.1215, we do not anticipate a change (decrease) in burden or costs to the laboratory because following the manufacturer's instructions for maintenance and function checks when using unmodified equipment, instruments, or test systems was acceptable practice for meeting the former requirement.

• In the specialty of histocompatibility now at § 493.1278, the laboratory's reagent typing inventory must indicate reagent specificity as well as the previously required source, bleeding date and identification number, and volume remaining. Indicating a reagent's specificity in the laboratory's reagent inventory is routine laboratory practice that was inadvertently not addressed in the regulations. This new requirement for documentation of reagent specificity will have no impact on the laboratory's burden or costs.

Revisions Resulting in a Decrease in Burden or Costs.

• We are eliminating the requirement under the specialty of histocompatibility for each individual performing testing to evaluate previously tested specimens monthly as specified formerly at § 493.1265. The mechanism for and frequency of competency assessment of histocompatibility testing personnel will now be determined, as it is in all other laboratory specialties and subspecialties, by the laboratory's technical consultant or supervisor under §§ 493.1413(b)(8) and (9) and 493.1449(b)(8) and (9), respectively. Although this is a reduction in burden, we cannot estimate the cost savings.

• For laboratories performing histocompatibility testing, we are eliminating the specified frequencies for screening potential transplant recipient sera for performed HLA–A and B antibodies (formerly at § 493.1265(a)(8)(i)). Instead, in this final rule at § 493.1278(d)(5), we are requiring the laboratory to have available and follow a policy, consistent with clinical transplant protocols, for the frequency of such antibody screening. While this is most likely a reduction in burden, we cannot estimate the cost savings, since emerging data and research information will be an ongoing factor in determining appropriate screening frequencies.

• For the performance of non-renal transplantation in an emergency situation, we are eliminating the requirement that the results of final crossmatches be available before the transplantation when the recipient demonstrates presensitization by prior serum screening. In this final rule at § 493.1278(f)(3) (formerly at § 493.1265(b)(3)), the laboratory must have available, and follow, policies that address when HLA testing and final crossmatches are required for presensitized non-renal transplant recipients. We cannot estimate the savings from this reduction.

Revisions for Which There May Be a Negligible Increase in Burden or Costs

• The laboratory must ensure a uni-directional workflow for molecular amplification systems that are not contained in enclosed systems. This includes maintaining physically separate areas for specimen preparation, amplification and product detection and reagent preparation, as applicable. This is a recommended guideline for good laboratory practice by several laboratory professional organizations. Although we are unable to estimate the number of laboratories that perform molecular amplification with open systems without following the recommended guideline, we expect the number to be small and any increase in burden or cost with meeting this new requirement, now at § 493.1101, negligible.

• If the laboratory ceases operation, it must make provisions to ensure that all records, slides, blocks, and tissues are maintained for the applicable time frames. We anticipate that this change now at § 493.1105 will affect few laboratories; however, we cannot estimate the number or associated cost.

• In the former requirements at §§ 493.911(c)(1), 493.913(c)(1), 493.915(c)(1), 493.917(c)(1), 493.919(c)(1), 493.923(b)(1), 493.927(c)(1), 493.931(c)(1), 493.933(c)(1), 493.937(c)(1), and 493.941(c)(1) PT programs were required to grade PT results by first comparing the laboratory's response to the response which reflects agreement of either 90 percent of 10 or more referee laboratories or 90 percent or more of all participating laboratories. If this consensus agreement requirement was met, then the results could be graded based on their values relative to the established correct response for each PT analyte, subspecialty, or specialty. If the consensus requirement was not met, then laboratories were not graded and received an acceptable score, by default. As a consequence of this, a portion of those laboratories receiving ungraded PT results may have failed to recognize that their actual PT performance was not acceptable and only realized that their performance was unacceptable when their PT results were reviewed as part of an inspection. Thus, in some instances laboratories failed to make appropriate corrections to testing problems, identified by unacceptable PT performance, in a timely manner. Now at §§ 493.911(c)(1), 493.913(c)(1), 493.915(c)(1), 493.917(c)(1), 493.919(c)(1), 493.923(b)(1), 493.927(c)(1), 493.931(c)(1), 493.933(c)(1), 493.937(c)(1), and 493.941(c)(1), the consensus agreement requirement is lowered to 80 percent. Fewer PT results will be ungraded and a portion of those laboratories previously not graded due to a lack of consensus will receive an unacceptable PT grade. Thus, these laboratories will be alerted to potential testing problems sooner. Also, with the change at § 493.1236(b)(2), which now requires all laboratories to verify testing accuracy for any analyte, subspecialty, or specialty assigned a PT score that does not reflect the laboratory's actual PT performance, an additional number of laboratories may become cognizant of their poor testing performance sooner than when PT results are not graded and they receive an acceptable score by default. The combination of fewer ungraded PT results with the requirement for all laboratories to review and verify their PT results, especially when they are deemed questionable by the PT program, will result in these laboratories, in a more timely manner, identifying and correcting potential sources of error which may not have been otherwise detected, thereby increasing overall laboratory accuracy. However, there may be some burden for those laboratories that are now required to verify testing accuracy but are having no real problem with testing. Since verifying testing accuracy whenever there is a potential likelihood of error is generally regarded as good laboratory practice, and in most instances the laboratory's routine use of QC may be used to verify testing accuracy, this should not be considered burdensome. Likewise, PT programs may be slightly inconvenienced by the need to change their grading algorithms to accommodate the 80 percent consensus requirement. However, it is the responsibility of PT programs to assist laboratories in assessing their testing performance by providing PT samples that can be appropriately graded.

Although these changes may affect laboratories and PT programs, the impact is not quantifiable and is considered minor compared to the overall beneficial effect of improved laboratory testing accuracy.

• Test requisitions or other written or electronic authorizations for testing must include the patient's sex and age or date of birth as specified now at § 493.1241. We expect a negligible increase in burden or cost because the patient's age or date of birth was required for Pap smears, formerly at § 493.1105(e), and most laboratories are already obtaining the patient's gender, since it is frequently necessary for appropriate test interpretation (as required formerly at § 493.1105(f)). The number of laboratories that have not been requesting the patient's gender and age or date of birth is unknown.

• The laboratory must use a control system capable of detecting reaction inhibition when performing molecular amplification procedures in which inhibition is a significant source of false negative results. This is a recommended guideline for good laboratory practice by several laboratory professional organizations and is now specified at § 493.1256(d)(3)(v). While we are unable to estimate the incidence of reaction inhibition or number of laboratories performing molecular amplification procedures without following the recommended guideline, we expect the number to be small and any increase in burden and/or cost with meeting this new requirement negligible.

• The laboratory must check immunohistochemical stains for positive and negative reactivity each time of use. Although this is an increase from the requirement (formerly at § 493.1259, now at § 493.1273(a)) to check special stains for positive reactivity, we cannot estimate the laboratory impact because we do not know the number of laboratories that perform immunohistochemical stains or how often the staining is performed. We expect this change to affect a small number of laboratories, and the increase in burden and costs will be small.

• In the specialty of clinical cytogenetics, sex determination must be performed by full chromosome analysis. Formerly, in clinical cytogenetics at § 493.1267(a) (now at § 493.1276(c)), full chromosome analysis was only required as a confirmatory test when the laboratory obtained atypical results on X and Y chromatin counts. Several commenters stated that due to the frequency of mosaicism in individuals with sex chromosome anueploidy, Barr body and ''Y'' body analysis is no longer considered the standard of practice for sex determination and should be eliminated from the cytogenetics laboratory test menu. Several laboratory professional organizations consider sex determination by full chromosome analysis the standard for good laboratory practice; therefore, we added this requirement. Although we are unable to estimate the number of cytogenetics laboratories that perform sex determination other than by full chromosome analysis, we expect the number to be small and any increase in burden or cost with meeting this requirement negligible.

• The requirements for the test report (formerly at § 493.1109, now at § 493.1291) must include the patient's name and identification number, or unique patient identifier and identification number; the test report date; and if appropriate, the specimen source. These are standard practices in most laboratories and the impact on burden or cost is expected to be minor.

In accordance with Executive Order 12866, this regulation was reviewed by the Office of Management and Budget.

References

Accreditation Committee for Graduate Medical Education, ''Number of all programs for a specific academic year Ending June 30, 2002.'' <*http://www.acgame.org/adspublic/reports/accredited_programs_all.asp*>. (April 23, 2002).

Ambulatory Sentinel Practice Network (ASPN). *Laboratory Medicine Questionnaire (Appendices 1 and 2)* 1996. Unpublished data.

American Association for Clinical Chemistry. ''Quality Assurance Alternatives for POCT.'' Audioconference, February 4, 1999.

American Board of Medical Specialties. ''General Certificates Issued 1991–2001, Table 2.'' September 2000. <*http://www.abms.org/statistics.asp*> (April 16, 2002).

American Board of Medical Specialties. ''Geographic Distribution of Diplomats by Speciality Certificate.'' September 2002. <*http://www.abms.org/statistics.asp*> (April 16, 2002).

American Medical Association, Center for Health Policy Research, ''Physician socioeconomic statistics,'' 2000–2002 edition, 2001.

American Society for Microbiology. ''Survey of quality control failures in the clinical microbiology laboratory.'' Report by Brenda McCurdy to the Clinical Laboratory Improvement Advisory Committee, September 25, 1996.

American Society for Microbiology. ''ASM benchmarking survey, microbiology productivity ''99.'' Report by Roberta Carey to the Clinical Laboratory Improvement Advisory Committee, September 22, 1999.

Astles, John R., Harvey B. Lipman, William O. Schalla, Sharon O. Blummer, Ronald F. Feld, Charlene Smith, Thomas L. Hearn. ''Impact of quality control on accuracy in enzyme immunoassay testing for human immunodeficiency virus type 1 antibodies.'' *Archives of Pathology and Laboratory Medicine* 122, 8 (1998), pp. 700–707.

Burman, William J., B.L. Stone, Randall R. Reves, *et al.* ''The incidence of false-positive cultures for Mycobacterium tuberculosis.'' *American Journal of Respiratory and Critical Care Medicine,* 155,1 (1997): pp. 321–326.

Bureau of Labor Statistics. *Occupational Outlook Handbook,* 2000–2001 edition.

Centers for Disease Control and Prevention. Laboratory practices for diagnosis of tuberculosis—United States, 1994. *Morbidity and Mortality Weekly Report* 1995, 44:587–590.

Eisenberg, Henry D., Ed. *Essential Procedures for Clinical Microbiology* (Chapter 4.8 Mycobacteriology—Identification Procedures from Culture, pp. 195–196), ASM Press, Washington, D.C., (1998).

Hoerger Thomas J., Jennifer L. Eggleston, Richard C. Lindrooth, and Emek Basker. ''Background report on the clinical laboratory industry. Final report.'' June 1997. Prepared by Centers for Economic Research, Research Triangle Institute, Research Triangle Institute, NC.

Huebner, Robin E., Robert C. Good, and Jerome I. Tokars. ''Current practices in mycobacteriology: results of a survey of state public health laboratories.'' *Journal of Clinical Microbiology* 31, 4 (1993), pp. 771–775.

Institute of Medicine (IOM), Committee on Medicare Payment Methodology for Clinical Laboratory Services. (2000). *Medical Laboratory Payment Policies, Now and in the Future (Appendix D).* Washington, DC: National Academy Press.

LaBeau, Kathleen M, Marianne Simon and Steven J. Steindel. ''The Pacific Northwest Laboratory Medicine Sentinel Monitoring Network.'' Final Report of the Findings of Questionnaire II, Test Volume and Menu Changes: 1997–1999.'' July 1999.

NCCLS Guideline EP 6–P. Evaluation of the linearity of quantitative analytical methods; proposed guideline. (1999). Villanova, PA: NCCLS.

NCCLS Document EP 15–P. User demonstration of performance for precision and accuracy; proposed guideline. (1998). Villanova, PA: NCCLS.

NCCLS Document C 28–A. How to define and determine reference intervals in the clinical laboratory; approved guideline. (1995). Villanova, PA: NCCLS.

Online Survey and Certification Reporting System (OSCAR). (Electronic database). (2001). Baltimore, MD: Centers for Medicare & Medicaid Services. (Producer and Distributor).

Steindel, Stephen J., William J. Rauch, Marianne K. Simon, and James Handsfield. ''National Inventory of Clinical Testing Services (NICLTS): development and test distribution for 1996.'' *Archives of Pathology and Laboratory Medicine* 124, (2000), pp. 1201–1208.

Tershakovec, Andrew M., S. Diane Brannon, Michael J. Bennett, and Barbara M. Shannon. ''The cost of implementation of

the Clinical Laboratory Improvement Amendments of 1988—the example of pediatric office-based cholesterol screening.'' *Pediatrics* 96, 2 (1995), pp. 230–234.

Ward-Cook, K., and Suzanne Tannar. ''2000 wage and vacancy survey of medical laboratories.'' *Laboratory Medicine* 32, 3, (2001), pp.124–138.

U.S. Government, Office of Personnel Management, Central Personnel Data File. ''Retirement Projections, Fiscal Years 2001–2005.'' *http://www.opm.gov/feddata/retire/rs-projections.pdf.* (April 16, 2002).

List of Subjects in 42 FR Part 493

Grant programs—health, Health facilities, Incorporation by Reference, Laboratories, Medicaid, Medicare, Reporting and recordkeeping requirements.

For the reasons set forth in the preamble, the Centers for Medicare & Medicaid Services is amending 42 CFR Chapter IV part 493 as set forth below:

PART 493—LABORATORY REQUIREMENTS

1. The authority citation for part 493 continues to read as follows:

Authority: Sec. 353 of the Public Health Service Act, secs. 1102, 1861(e), the sentence following sections 1861(s)(11) through 1861(s)(16) of the Social Security Act (42 U.S.C. 263a, 1302, 1395x(e), and the sentence following 1395x(s)(11) through 1395x(s)(16)).

Subpart A—General Provisions

2. In § 493.2, the introductory text is republished, and the following definitions are added in alphabetical order to read as follows:

§ 493.2 Definitions

As used in this part, unless the context indicates otherwise—

* * * * *

Calibration means a process of testing and adjusting an instrument or test system to establish a correlation between the measurement response and the concentration or amount of the substance that is being measured by the test procedure.

Calibration verification means the assaying of materials of known concentration in the same manner as patient samples to substantiate the instrument or test system's calibration throughout the reportable range for patient test results.

* * * * *

FDA-cleared or approved test system means a test system cleared or approved by the FDA through the premarket notification (510(k)) or premarket approval (PMA) process for in-vitro diagnostic use. Unless otherwise stated, this includes test systems exempt from FDA premarket clearance or approval.

* * * * *

Reportable range means the span of test result values over which the laboratory can establish or verify the accuracy of the instrument or test system measurement response.

* * * * *

Test system means the instructions and all of the instrumentation, equipment, reagents, and supplies needed to perform an assay or examination and generate test results.

* * * * *

§ 493.3 [Amended]

3. Amend § 493.3, as follows:

a. In paragraph(b)(3), remove the words ''National Institutes on Drug Abuse (NIDA)'' and add, in their place, the words ''Substance Abuse and Mental Health Services Administration (SAMHSA)''.

b. In paragraph (b)(3), remove the word ''NIDA'' and add, in its place, the word ''SAMHSA''.

§ 493.20 [Amended]

3a. Amend § 493.20, as follows:

a. In paragraph (b), remove the reference to ''subpart P''.

b. In paragraph (b), remove the cross reference to ''§ 493.1777'' and add, in its place ''§§ 493.1773 and 493.1777''.

c. In paragraph (c), remove the cross reference to ''§§ 493.15(e) and 493.1775'' and add, in its place, ''§§ 493.15(e), 493.1773, and 493.1775''.

§ 493.25 [Amended]

4. Amend § 493.25 as follows:

a. In paragraph (b), remove the reference to ''subpart P''.

b. In paragraph (c), remove the reference to ''subpart P''.

c. In paragraph (c), remove ''§ 493.1777'' and add, in its place, ''§§ 493.1773 and 493.1777''.

d. In paragraph (d), remove the reference to ''subpart P''.

e. In paragraph (d), remove the cross reference to ''§§ 493.15(e) and 493.1775'' and add, in its place, ''§§ 493.15(e), 493.1773, and 493.1775''.

Subpart C—Registration Certificate, Certificate for Provider-Performed Microscopy Procedures, and Certificate of Compliance

§ 493.43 [Amended]

6. In § 493.43(a), remove the words ''tests of moderate complexity (including the subcategory) or high complexity, or any combination of these tests,'' and add, in their place, the words ''nonwaived testing''.

§ 493.45 [Amended]

7. In § 493.45(c)(3), remove the reference to ''subpart P''.

§ 493.47 [Amended]

8. Amend § 493.47 as follows:

a. In paragraph (c)(2), remove the reference to ''subpart P''.

b. In paragraph (c)(3), remove the cross reference to ''§ 493.1776'' and add, in its place, ''§§ 493.1773 and 493.1775''.

§ 493.49 [Amended]

9. In § 493.49(a)(3), remove the reference to ''subpart P''.

Subpart F—General Administration

§ 493.643 [Amended]

10. In § 493.643(c)(3)(ix), add the word ''Clinical'' before the word ''Cytogenetics''.

Subpart H—Participation in Proficiency Testing for Laboratories Performing Nonwaived Testing

11. Revise the heading of Subpart H to read as set forth above.

§ 493.801 [Amended]

12. In § 493.801(a)(2)(ii), remove the cross reference to ''§ 493.1709'' and add, in its place, ''§ 493.1236(c)(1)''.

§ 493.803 [Amended]

13. In § 493.803(a), remove the words ''tests of moderate complexity (including the subcategory) and/or high complexity'' and add, in their place, the words ''nonwaived testing''.

§ 493.807 [Amended]

14. Revise the heading of §493.807 to read as follows:

§ 493.807 Condition: Reinstatement of laboratories performing nonwaived testing.

Subpart I—Proficiency Testing Programs for Nonwaived Testing

15. Revise the heading of subpart I to read as set forth above.

§§ 493.911, 493.913, 493.915, 493.917, 493.919, 493.923, 493.927, 493.931, 493.933, 493.937, and 493.941 [Amended]

16. In §§ 493.911(c)(1), 493.913(c)(1), 493.915(c)(1), 493.917(c)(1), 493.919(c)(1), 493.923(b)(1), 493.927(c)(1), 493.931(c)(1), 493.933(c)(1), 493.937(c)(1), and 493.941(c)(1), remove ''90 percent'' and add, in its place, ''80 percent'' wherever it appears.

§ 493.945 [Amended]

17. In § 493.945(a)(1), remove ''§ 493.1257'' and add, in its place,

''§§ 493.1105(a)(7)(i)(A) and 493.1274(f)(2)''.

18. Subpart J, consisting of §§ 493.1100 through 493.1105, and subpart K, consisting of §§ 493.1200 through 493.1299, are revised to read as follows:

Subpart J—Facility Administration for Nonwaived Testing

Subpart K—Quality Systems for Nonwaived Testing

Subpart J—Facility Administration for Nonwaived Testing

§ 493.1100 Condition: Facility administration.

Each laboratory that performs nonwaived testing must meet the applicable requirements under §§ 493.1101 through 493.1105, unless HHS approves a procedure that provides equivalent quality testing as specified in Appendix C of the State Operations Manual (CMS Pub. 7).

§ 493.1101 Standard: Facilities.

(a) The laboratory must be constructed, arranged, and maintained to ensure the following:

(1) The space, ventilation, and utilities necessary for conducting all phases of the testing process.

(2) Contamination of patient specimens, equipment, instruments, reagents, materials, and supplies is minimized.

(3) Molecular amplification procedures that are not contained in closed systems have a uni-directional workflow. This must include separate areas for specimen preparation, amplification and product detection, and, as applicable, reagent preparation.

(b) The laboratory must have appropriate and sufficient equipment, instruments, reagents, materials, and supplies for the type and volume of testing it performs.

(c) The laboratory must be in compliance with applicable Federal, State, and local laboratory requirements.

(d) Safety procedures must be established, accessible, and observed to ensure protection from physical, chemical, biochemical, and electrical hazards, and biohazardous materials.

(e) Records and, as applicable, slides, blocks, and tissues must be maintained and stored under conditions that ensure proper preservation.

§ 493.1103 Standard: Requirements for transfusion services.

A facility that provides transfusion services must meet all of the requirements of this section and document all transfusion-related activities.

(a) *Arrangement for services.* The facility must have a transfusion service agreement reviewed and approved by the responsible party(ies) that govern the procurement, transfer, and availability of blood and blood products.

(b) *Provision of testing.* The facility must provide prompt ABO grouping, D(Rho) typing, unexpected antibody detection, compatibility testing, and laboratory investigation of transfusion reactions on a continuous basis through a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by CMS.

(c) *Blood and blood products storage and distribution.* (1) If a facility stores or maintains blood or blood products for transfusion outside of a monitored refrigerator, the facility must ensure the storage conditions, including temperature, are appropriate to prevent deterioration of the blood or blood product.

(2) The facility must establish and follow policies to ensure positive identification of a blood or blood product recipient.

(d) *Investigation of transfusion reactions.* The facility must have procedures for preventing transfusion reactions and when necessary, promptly identify, investigate, and report blood and blood product transfusion reactions to the laboratory and, as appropriate, to Federal and State authorities.

§ 493.1105 Standard: Retention requirements.

(a) The laboratory must retain its records and, as applicable, slides, blocks, and tissues as follows:

(1) *Test requisitions and authorizations.* Retain records of test requisitions and test authorizations, including the patient's chart or medical record if used as the test requisition or authorization, for at least 2 years.

(2) *Test procedures.* Retain a copy of each test procedure for at least 2 years after a procedure has been discontinued. Each test procedure must include the dates of initial use and discontinuance.

(3) *Analytic systems records.* Retain quality control and patient test records (including instrument printouts, if applicable) and all analytic systems activities specified in §§ 493.1252 through 493.1289 for at least 2 years. In addition, retain the following:

(i) Records of test system performance specifications that the laboratory establishes or verifies under § 493.1253 for the period of time the laboratory uses the test system but no less than 2 years.

(ii) Immunohematology records, blood and blood product records, and transfusion records as specified in 21 CFR 606.160(b)(3)(ii), (b)(3)(v), and (d).

(4) *Proficiency testing records.* Retain all proficiency testing records for at least 2 years.

(5) *Laboratory quality systems assessment records.* Retain all laboratory quality systems assessment records for at least 2 years.

(6) *Test reports.* Retain or be able to retrieve a copy of the original report (including final, preliminary, and corrected reports) at least 2 years after the date of reporting. In addition, retain the following:

(i) Immunohematology reports as specified in 21 CFR 606.160(b)(3)(ii), (b)(3)(iv), and (d).

(ii) Pathology test reports for at least 10 years after the date of reporting.

(7) *Slide, block, and tissue retention—*

(i) *Slides.*

(A) Retain cytology slide preparations for at least 5 years from the date of examination (see § 493.1274(f) for proficiency testing exception).

(B) Retain histopathology slides for at least 10 years from the date of examination.

(ii) *Blocks.* Retain pathology specimen blocks for at least 2 years from the date of examination.

(iii) *Tissue.* Preserve remnants of tissue for pathology examination until a diagnosis is made on the specimen.

(b) If the laboratory ceases operation, the laboratory must make provisions to ensure that all records and, as applicable, slides, blocks, and tissue are maintained and available for the time frames specified in this section.

Subpart K—Quality Systems for Nonwaived Testing

§ 493.1200 Introduction.

(a) Each laboratory that performs nonwaived testing must establish and maintain written policies and procedures that implement and monitor quality systems for all phases of the total testing process (that is, preanalytic, analytic, and postanalytic) as well as general laboratory systems.

(b) Each of the laboratory's quality systems must include an assessment component that ensures continuous improvement of the laboratory's performance and services through ongoing monitoring that identifies, evaluates and resolves problems.

(c) The various components of the laboratory's quality systems are used to meet the requirements in this part and must be appropriate for the specialties and subspecialties of testing the laboratory performs, services it offers, and clients it serves.

§ 493.1201 Condition: Bacteriology.

If the laboratory provides services in the subspecialty of Bacteriology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1261, and §§ 493.1281 through 493.1299.

§ 493.1202 Condition: Mycobacteriology.

If the laboratory provides services in the subspecialty of Mycobacteriology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1262, and §§ 493.1281 through 493.1299.

§ 493.1203 Condition: Mycology.

If the laboratory provides services in the subspecialty of Mycology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1263, and §§ 493.1281 through 493.1299.

§ 493.1204 Condition: Parasitology.

If the laboratory provides services in the subspecialty of Parasitology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1264, and §§ 493.1281 through 493.1299.

§ 493.1205 Condition: Virology.

If the laboratory provides services in the subspecialty of Virology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1265, and §§ 493.1281 through 493.1299.

§ 493.1207 Condition: Syphilis serology.

If the laboratory provides services in the subspecialty of Syphilis serology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1208 Condition: General immunology.

If the laboratory provides services in the subspecialty of General immunology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 93.1281 through 493.1299.

§ 493.1210 Condition: Routine chemistry.

If the laboratory provides services in the subspecialty of Routine chemistry, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1267, and §§ 493.1281 through 493.1299.

§ 493.1211 Condition: Urinalysis.

If the laboratory provides services in the subspecialty of Urinalysis, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1212 Condition: Endocrinology.

If the laboratory provides services in the subspecialty of Endocrinology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1213 Condition: Toxicology.

If the laboratory provides services in the subspecialty of Toxicology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1215 Condition: Hematology.

If the laboratory provides services in the specialty of Hematology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1269, and §§ 493.1281 through 493.1299.

§ 493.1217 Condition: Immunohematology.

If the laboratory provides services in the specialty of Immunohematology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1271, and §§ 493.1281 through 493.1299.

§ 493.1219 Condition: Histopathology.

If the laboratory provides services in the subspecialty of Histopathology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1273, and §§ 493.1281 through 493.1299.

§ 493.1220 Condition: Oral pathology.

If the laboratory provides services in the subspecialty of Oral pathology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1221 Condition: Cytology.

If the laboratory provides services in the subspecialty of Cytology, the

laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1274, and §§ 493.1281 through 493.1299.

§ 493.1225 Condition: Clinical cytogenetics.

If the laboratory provides services in the specialty of Clinical cytogenetics, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1276, and §§ 493.1281 through 493.1299.

§ 493.1226 Condition: Radiobioassay.

If the laboratory provides services in the specialty of Radiobioassay, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1227 Condition: Histocompatibility.

If the laboratory provides services in the specialty of Histocompatibility, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1278, and §§ 493.1281 through 493.1299.

General Laboratory Systems

§ 493.1230 Condition: General laboratory systems.

Each laboratory that performs nonwaived testing must meet the applicable general laboratory systems requirements in §§ 493.1231 through 493.1236, unless HHS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7), that provides equivalent quality testing. The laboratory must monitor and evaluate the overall quality of the general laboratory systems and correct identified problems as specified in § 493.1239 for each specialty and subspecialty of testing performed.

§ 493.1231 Standard: Confidentiality of patient information.

The laboratory must ensure confidentiality of patient information throughout all phases of the total testing process that are under the laboratory's control.

§ 493.1232 Standard: Specimen identification and integrity.

The laboratory must establish and follow written policies and procedures that ensure positive identification and optimum integrity of a patient's specimen from the time of collection or receipt of the specimen through completion of testing and reporting of results.

§ 493.1233 Standard: Complaint investigations.

The laboratory must have a system in place to ensure that it documents all complaints and problems reported to the laboratory. The laboratory must conduct investigations of complaints, when appropriate.

§ 493.1234 Standard: Communications.

The laboratory must have a system in place to identify and document problems that occur as a result of a breakdown in communication between the laboratory and an authorized individual who orders or receives test results.

§ 493.1235 Standard: Personnel competency assessment policies.

As specified in the personnel requirements in subpart M, the laboratory must establish and follow written policies and procedures to assess employee and, if applicable, consultant competency.

§ 493.1236 Standard: Evaluation of proficiency testing performance.

(a) The laboratory must review and evaluate the results obtained on proficiency testing performed as specified in subpart H of this part.

(b) The laboratory must verify the accuracy of the following:

(1) Any analyte or subspecialty without analytes listed in subpart I of this part that is not evaluated or scored by a CMS-approved proficiency testing program.

(2) Any analyte, specialty or subspecialty assigned a proficiency testing score that does not reflect laboratory test performance (that is, when the proficiency testing program does not obtain the agreement required for scoring as specified in subpart I of this part, or the laboratory receives a zero score for nonparticipation, or late return of results).

(c) At least twice annually, the laboratory must verify the accuracy of the following:

(1) Any test or procedure it performs that is not included in subpart I of this part.

(2) Any test or procedure listed in subpart I of this part for which compatible proficiency testing samples are not offered by a CMS-approved proficiency testing program.

(d) All proficiency testing evaluation and verification activities must be documented.

§ 493.1239 Standard: General laboratory systems assessment.

(a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and, when indicated, correct problems identified in the general laboratory system requirements specified at §§ 493.1231 through 493.1236.

(b) The general laboratory systems assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of general laboratory systems assessment reviews with appropriate staff.

(c) The laboratory must document all general laboratory systems assessment activities.

Preanalytic Systems

§ 493.1240 Condition: Preanalytic systems.

Each laboratory that performs nonwaived testing must meet the applicable preanalytic system(s) requirements in §§ 493.1241 and 493.1242, unless HHS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7), that provides equivalent quality testing. The laboratory must monitor and evaluate the overall quality of the preanalytic systems and correct identified problems as specified in § 493.1249 for each specialty and subspecialty of testing performed.

§ 493.1241 Standard: Test request.

(a) The laboratory must have a written or electronic request for patient testing from an authorized person.

(b) The laboratory may accept oral requests for laboratory tests if it solicits a written or electronic authorization within 30 days of the oral request and maintains the authorization or documentation of its efforts to obtain the authorization.

(c) The laboratory must ensure the test requisition solicits the following information:

(1) The name and address or other suitable identifiers of the authorized person requesting the test and, if appropriate, the individual responsible for using the test results, or the name and address of the laboratory submitting the specimen, including, as applicable, a contact person to enable the reporting of imminently life threatening laboratory results or panic or alert values.

(2) The patient's name or unique patient identifier.

(3) The sex and age or date of birth of the patient.

(4) The test(s) to be performed.

(5) The source of the specimen, when appropriate.

(6) The date and, if appropriate, time of specimen collection.

(7) For Pap smears, the patient's last menstrual period, and indication of whether the patient had a previous abnormal report, treatment, or biopsy.

(8) Any additional information relevant and necessary for a specific test to ensure accurate and timely testing and reporting of results, including interpretation, if applicable.

(d) The patient's chart or medical record may be used as the test requisition or authorization but must be available to the laboratory at the time of testing and available to CMS or a CMS agent upon request.

(e) If the laboratory transcribes or enters test requisition or authorization information into a record system or a laboratory information system, the laboratory must ensure the information is transcribed or entered accurately.

§ 493.1242 Standard: Specimen submission, handling, and referral.

(a) The laboratory must establish and follow written policies and procedures for each of the following, if applicable:

(1) Patient preparation.

(2) Specimen collection.

(3) Specimen labeling, including patient name or unique patient identifier and, when appropriate, specimen source.

(4) Specimen storage and preservation.

(5) Conditions for specimen transportation.

(6) Specimen processing.

(7) Specimen acceptability and rejection.

(8) Specimen referral.

(b) The laboratory must document the date and time it receives a specimen.

(c) The laboratory must refer a specimen for testing only to a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by CMS.

(d) If the laboratory accepts a referral specimen, written instructions must be available to the laboratory's clients and must include, as appropriate, the information specified in paragraphs (a)(1) through (a)(7) of this section.

§ 493.1249 Standard: Preanalytic systems assessment.

(a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the preanalytic systems specified at §§ 493.1241 through 493.1242.

(b) The preanalytic systems assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of preanalytic systems assessment reviews with appropriate staff.

(c) The laboratory must document all preanalytic systems assessment activities.

Analytic Systems

§ 493.1250 Condition: Analytic systems.

Each laboratory that performs nonwaived testing must meet the applicable analytic systems requirements in §§ 493.1251 through 493.1283, unless HHS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7), that provides equivalent quality testing. The laboratory must monitor and evaluate the overall quality of the analytic systems and correct identified problems as specified in § 493.1289 for each specialty and subspecialty of testing performed.

§ 493.1251 Standard: Procedure manual.

(a) A written procedure manual for all tests, assays, and examinations performed by the laboratory must be available to, and followed by, laboratory personnel. Textbooks may supplement but not replace the laboratory's written procedures for testing or examining specimens.

(b) The procedure manual must include the following when applicable to the test procedure:

(1) Requirements for patient preparation; specimen collection, labeling, storage, preservation, transportation, processing, and referral; and criteria for specimen acceptability and rejection as described in § 493.1242.

(2) Microscopic examination, including the detection of inadequately prepared slides.

(3) Step-by-step performance of the procedure, including test calculations and interpretation of results.

(4) Preparation of slides, solutions, calibrators, controls, reagents, stains, and other materials used in testing.

(5) Calibration and calibration verification procedures.

(6) The reportable range for test results for the test system as established or verified in § 493.1253.

(7) Control procedures.

(8) Corrective action to take when calibration or control results fail to meet the laboratory's criteria for acceptability.

(9) Limitations in the test methodology, including interfering substances.

(10) Reference intervals (normal values).

(11) Imminently life-threatening test results or panic or alert values.

(12) Pertinent literature references.

(13) The laboratory's system for entering results in the patient record and reporting patient results including, when appropriate, the protocol for reporting imminent life threatening results, or panic, or alert values.

(14) Description of the course of action to take if a test system becomes inoperable.

(c) Manufacturer's test system instructions or operator manuals may be used, when applicable, to meet the requirements of paragraphs (b)(1) through (b)(12) of this section. Any of the items under paragraphs (b)(1) through (b)(12) of this section not provided by the manufacturer must be provided by the laboratory.

(d) Procedures and changes in procedures must be approved, signed, and dated by the current laboratory director before use.

(e) The laboratory must maintain a copy of each procedure with the dates of initial use and discontinuance as described in § 493.1105(a)(2).

§ 493.1252 Standard: Test systems, equipment, instruments, reagents, materials, and supplies.

(a) Test systems must be selected by the laboratory. The testing must be performed following the manufacturer's instructions and in a manner that provides test results within the laboratory's stated performance specifications for each test system as determined under § 493.1253.

(b) The laboratory must define criteria for those conditions that are essential for proper storage of reagents and specimens, accurate and reliable test system operation, and test result reporting. The criteria must be consistent with the manufacturer's instructions, if provided. These conditions must be monitored and documented and, if applicable, include the following:

(1) Water quality.

(2) Temperature.

(3) Humidity.

(4) Protection of equipment and instruments from fluctuations and interruptions in electrical current that adversely affect patient test results and test reports.

(c) Reagents, solutions, culture media, control materials, calibration materials, and other supplies, as appropriate, must be labeled to indicate the following:

(1) Identity and when significant, titer, strength or concentration.

(2) Storage requirements.

(3) Preparation and expiration dates.

(4) Other pertinent information required for proper use.

(d) Reagents, solutions, culture media, control materials, calibration materials,

and other supplies must not be used when they have exceeded their expiration date, have deteriorated, or are of substandard quality.

(e) Components of reagent kits of different lot numbers must not be interchanged unless otherwise specified by the manufacturer.

§ 493.1253 Standard: Establishment and verification of performance specifications.

(a) *Applicability.* Laboratories are not required to verify or establish performance specifications for any test system used by the laboratory before April 24, 2003.

(b)(1) *Verification of performance specifications.* Each laboratory that introduces an unmodified, FDA-cleared or approved test system must do the following before reporting patient test results:

(i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics:

(A) Accuracy.

(B) Precision.

(C) Reportable range of test results for the test system.

(ii) Verify that the manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population.

(2) *Establishment of performance specifications.* Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures, Gram stain, or potassium hydroxide preparations), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable:

(i) Accuracy.

(ii) Precision.

(iii) Analytical sensitivity.

(iv) Analytical specificity to include interfering substances.

(v) Reportable range of test results for the test system.

(vi) Reference intervals (normal values).

(vii) Any other performance characteristic required for test performance.

(3) *Determination of calibration and control procedures.* The laboratory must determine the test system's calibration procedures and control procedures based upon the performance specifications verified or established under paragraph (b)(1) or (b)(2) of this section.

(c) *Documentation.* The laboratory must document all activities specified in this section.

§ 493.1254 Standard: Maintenance and function checks.

(a) *Unmodified manufacturer's equipment, instruments, or test systems.* The laboratory must perform and document the following:

(1) Maintenance as defined by the manufacturer and with at least the frequency specified by the manufacturer.

(2) Function checks as defined by the manufacturer and with at least the frequency specified by the manufacturer. Function checks must be within the manufacturer's established limits before patient testing is conducted.

(b) *Equipment, instruments, or test systems developed in-house, commercially available and modified by the laboratory, or maintenance and function check protocols are not provided by the manufacturer.* The laboratory must do the following:

(1)(i) Establish a maintenance protocol that ensures equipment, instrument, and test system performance that is necessary for accurate and reliable test results and test result reporting.

(ii) Perform and document the maintenance activities specified in paragraph (b)(1)(i) of this section.

(2)(i) Define a function check protocol that ensures equipment, instrument, and test system performance that is necessary for accurate and reliable test results and test result reporting.

(ii) Perform and document the function checks, including background or baseline checks, specified in paragraph (b)(2)(i) of this section. Function checks must be within the laboratory's established limits before patient testing is conducted.

§ 493.1255 Standard: Calibration and calibration verification procedures.

Calibration and calibration verification procedures are required to substantiate the continued accuracy of the test system throughout the laboratory's reportable range of test results for the test system. Unless otherwise specified in this subpart, for each applicable test system the laboratory must do the following:

(a) Perform and document calibration procedures—

(1) Following the manufacturer's test system instructions, using calibration materials provided or specified, and with at least the frequency recommended by the manufacturer;

(2) Using the criteria verified or established by the laboratory as specified in § 493.1253(b)(3)—

(i) Using calibration materials appropriate for the test system and, if possible, traceable to a reference method or reference material of known value; and

(ii) Including the number, type, and concentration of calibration materials, as well as acceptable limits for and the frequency of calibration; and

(3) Whenever calibration verification fails to meet the laboratory's acceptable limits for calibration verification.

(b) Perform and document calibration verification procedures—

(1) Following the manufacturer's calibration verification instructions;

(2) Using the criteria verified or established by the laboratory under § 493.1253(b)(3)—

(i) Including the number, type, and concentration of the materials, as well as acceptable limits for calibration verification; and

(ii) Including at least a minimal (or zero) value, a mid-point value, and a maximum value near the upper limit of the range to verify the laboratory's reportable range of test results for the test system; and

(3) At least once every 6 months and whenever any of the following occur:

(i) A complete change of reagents for a procedure is introduced, unless the laboratory can demonstrate that changing reagent lot numbers does not affect the range used to report patient test results, and control values are not adversely affected by reagent lot number changes.

(ii) There is major preventive maintenance or replacement of critical parts that may influence test performance.

(iii) Control materials reflect an unusual trend or shift, or are outside of the laboratory's acceptable limits, and other means of assessing and correcting unacceptable control values fail to identify and correct the problem.

(iv) The laboratory's established schedule for verifying the reportable range for patient test results requires more frequent calibration verification.

§ 493.1256 Standard: Control procedures.

(a) For each test system, the laboratory is responsible for having control procedures that monitor the accuracy and precision of the complete analytical process.

(b) The laboratory must establish the number, type, and frequency of testing control materials using, if applicable, the performance specifications verified

or established by the laboratory as specified in § 493.1253(b)(3).

(c) The control procedures must—

(1) Detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance.

(2) Monitor over time the accuracy and precision of test performance that may be influenced by changes in test system performance and environmental conditions, and variance in operator performance.

(d) Unless CMS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7), that provides equivalent quality testing, the laboratory must—

(1) Perform control procedures as defined in this section unless otherwise specified in the additional specialty and subspecialty requirements at §§ 493.1261 through 493.1278.

(2) For each test system, perform control procedures using the number and frequency specified by the manufacturer or established by the laboratory when they meet or exceed the requirements in paragraph (d)(3) of this section.

(3) At least once each day patient specimens are assayed or examined perform the following for—

(i) Each quantitative procedure, include two control materials of different concentrations;

(ii) Each qualitative procedure, include a negative and positive control material;

(iii) Test procedures producing graded or titered results, include a negative control material and a control material with graded or titered reactivity, respectively;

(iv) Each test system that has an extraction phase, include two control materials, including one that is capable of detecting errors in the extraction process; and

(v) Each molecular amplification procedure, include two control materials and, if reaction inhibition is a significant source of false negative results, a control material capable of detecting the inhibition.

(4) For thin layer chromatography—

(i) Spot each plate or card, as applicable, with a calibrator containing all known substances or drug groups, as appropriate, which are identified by thin layer chromatography and reported by the laboratory; and

(ii) Include at least one control material on each plate or card, as applicable, which must be processed through each step of patient testing, including extraction processes.

(5) For each electrophoretic procedure include, concurrent with patient specimens, at least one control material containing the substances being identified or measured.

(6) Perform control material testing as specified in this paragraph before resuming patient testing when a complete change of reagents is introduced; major preventive maintenance is performed; or any critical part that may influence test performance is replaced.

(7) Over time, rotate control material testing among all operators who perform the test.

(8) Test control materials in the same manner as patient specimens.

(9) When using calibration material as a control material, use calibration material from a different lot number than that used to establish a cut-off value or to calibrate the test system.

(10) Establish or verify the criteria for acceptability of all control materials.

(i) When control materials providing quantitative results are used, statistical parameters (for example, mean and standard deviation) for each batch and lot number of control materials must be defined and available.

(ii) The laboratory may use the stated value of a commercially assayed control material provided the stated value is for the methodology and instrumentation employed by the laboratory and is verified by the laboratory.

(iii) Statistical parameters for unassayed control materials must be established over time by the laboratory through concurrent testing of control materials having previously determined statistical parameters.

(e) For reagent, media, and supply checks, the laboratory must do the following:

(1) Check each batch (prepared in-house), lot number (commercially prepared) and shipment of reagents, disks, stains, antisera, and identification systems (systems using two or more substrates or two or more reagents, or a combination) when prepared or opened for positive and negative reactivity, as well as graded reactivity, if applicable.

(2) Each day of use (unless otherwise specified in this subpart), test staining materials for intended reactivity to ensure predictable staining characteristics. Control materials for both positive and negative reactivity must be included, as appropriate.

(3) Check fluorescent and immunohistochemical stains for positive and negative reactivity each time of use.

(4) Before, or concurrent with the initial use—

(i) Check each batch of media for sterility if sterility is required for testing;

(ii) Check each batch of media for its ability to support growth and, as appropriate, select or inhibit specific organisms or produce a biochemical response; and

(iii) Document the physical characteristics of the media when compromised and report any deterioration in the media to the manufacturer.

(5) Follow the manufacturer's specifications for using reagents, media, and supplies and be responsible for results.

(f) Results of control materials must meet the laboratory's and, as applicable, the manufacturer's test system criteria for acceptability before reporting patient test results.

(g) The laboratory must document all control procedures performed.

(h) If control materials are not available, the laboratory must have an alternative mechanism to detect immediate errors and monitor test system performance over time. The performance of alternative control procedures must be documented.

§ 493.1261 Standard: Bacteriology.

(a) The laboratory must check the following for positive and negative reactivity using control organisms:

(1) Each day of use for beta-lactamase methods other than Cefinase™.

(2) Each week of use for Gram stains.

(3) When each batch (prepared in-house), lot number (commercially prepared), and shipment of antisera is prepared or opened, and once every 6 months thereafter.

(b) For antimicrobial susceptibility tests, the laboratory must check each batch of media and each lot number and shipment of antimicrobial agent(s) before, or concurrent with, initial use, using approved control organisms.

(1) Each day tests are performed, the laboratory must use the appropriate control organism(s) to check the procedure.

(2) The laboratory's zone sizes or minimum inhibitory concentration for control organisms must be within established limits before reporting patient results.

(c) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1262 Standard: Mycobacteriology.

(a) Each day of use, the laboratory must check all reagents or test procedures used for mycobacteria identification with at least one acid-fast organism that produces a positive reaction and an acid-fast organism that produces a negative reaction.

(b) For antimycobacterial susceptibility tests, the laboratory must

check each batch of media and each lot number and shipment of antimycobacterial agent(s) before, or concurrent with, initial use, using an appropriate control organism(s).

(1) The laboratory must establish limits for acceptable control results.

(2) Each week tests are performed, the laboratory must use the appropriate control organism(s) to check the procedure.

(3) The results for the control organism(s) must be within established limits before reporting patient results.

(c) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1263 Standard: Mycology.

(a) The laboratory must check each batch (prepared in-house), lot number (commercially prepared), and shipment of lactophenol cotton blue when prepared or opened for intended reactivity with a control organism(s).

(b) For antifungal susceptibility tests, the laboratory must check each batch of media and each lot number and shipment of antifungal agent(s) before, or concurrent with, initial use, using an appropriate control organism(s).

(1) The laboratory must establish limits for acceptable control results.

(2) Each day tests are performed, the laboratory must use the appropriate control organism(s) to check the procedure.

(3) The results for the control organism(s) must be within established limits before reporting patient results.

(c) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1264 Standard: Parasitology.

(a) The laboratory must have available a reference collection of slides or photographs and, if available, gross specimens for identification of parasites and use these references in the laboratory for appropriate comparison with diagnostic specimens.

(b) The laboratory must calibrate and use the calibrated ocular micrometer for determining the size of ova and parasites, if size is a critical parameter.

(c) Each month of use, the laboratory must check permanent stains using a fecal sample control material that will demonstrate staining characteristics.

(d) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1265 Standard: Virology.

(a) When using cell culture to isolate or identify viruses, the laboratory must simultaneously incubate a cell substrate control or uninoculated cells as a negative control material.

(b) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1267 Standard: Routine chemistry.

For blood gas analyses, the laboratory must perform the following:

(a) Calibrate or verify calibration according to the manufacturer's specifications and with at least the frequency recommended by the manufacturer.

(b) Test one sample of control material each 8 hours of testing using a combination of control materials that include both low and high values on each day of testing.

(c) Test one sample of control material each time specimens are tested unless automated instrumentation internally verifies calibration at least every 30 minutes.

(d) Document all control procedures performed, as specified in this section.

§ 493.1269 Standard: Hematology.

(a) For manual cell counts performed using a hemocytometer—

(1) One control material must be tested each 8 hours of operation; and

(2) Patient specimens and control materials must be tested in duplicate.

(b) For all nonmanual coagulation test systems, the laboratory must include two levels of control material each 8 hours of operation and each time a reagent is changed.

(c) For manual coagulation tests—

(1) Each individual performing tests must test two levels of control materials before testing patient samples and each time a reagent is changed; and

(2) Patient specimens and control materials must be tested in duplicate.

(d) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1271 Standard: Immunohematology.

(a) *Patient testing.* (1) The laboratory must perform ABO grouping, D(Rho) typing, unexpected antibody detection, antibody identification, and compatibility testing by following the manufacturer's instructions, if provided, and as applicable, 21 CFR 606.151(a) through (e).

(2) The laboratory must determine ABO group by concurrently testing unknown red cells with, at a minimum, anti-A and anti-B grouping reagents. For confirmation of ABO group, the unknown serum must be tested with known A1 and B red cells.

(3) The laboratory must determine the D(Rho) type by testing unknown red cells with anti-D (anti-Rho) blood typing reagent.

(b) *Immunohematological testing and distribution of blood and blood products.* Blood and blood product testing and distribution must comply with 21 CFR 606.100(b)(12); 606.160(b)(3)(ii) and (b)(3)(v); 610.40; 640.5(a), (b), (c), and (e); and 640.11(b).

(c) *Blood and blood products storage.* Blood and blood products must be stored under appropriate conditions that include an adequate temperature alarm system that is regularly inspected.

(1) An audible alarm system must monitor proper blood and blood product storage temperature over a 24-hour period.

(2) Inspections of the alarm system must be documented.

(d) *Retention of samples of transfused blood.* According to the laboratory's established procedures, samples of each unit of transfused blood must be retained for further testing in the event of transfusion reactions. The laboratory must promptly dispose of blood not retained for further testing that has passed its expiration date.

(e) *Investigation of transfusion reactions.* (1) According to its established procedures, the laboratory that performs compatibility testing, or issues blood or blood products, must promptly investigate all transfusion reactions occurring in facilities for which it has investigational responsibility and make recommendations to the medical staff regarding improvements in transfusion procedures.

(2) The laboratory must document, as applicable, that all necessary remedial actions are taken to prevent recurrences of transfusion reactions and that all policies and procedures are reviewed to assure they are adequate to ensure the safety of individuals being transfused.

(f) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1273 Standard: Histopathology.

(a) Fluorescent and immunohistochemical stains must be checked for positive and negative reactivity each time of use. For all other differential or special stains, a control slide of known reactivity must be stained with each patient slide or group of patient slides. Reaction(s) of the control slide with each special stain must be documented.

(b) The laboratory must retain stained slides, specimen blocks, and tissue remnants as specified in § 493.1105. The remnants of tissue specimens must be maintained in a manner that ensures proper preservation of the tissue specimens until the portions submitted for microscopic examination have been examined and a diagnosis made by an

individual qualified under §§ 493.1449(b), (l), or (m).

(c) An individual who has successfully completed a training program in neuromuscular pathology approved by HHS may examine and provide reports for neuromuscular pathology.

(d) Tissue pathology reports must be signed by an individual qualified as specified in paragraph (b) or, as appropriate, paragraph (c) of this section. If a computer report is generated with an electronic signature, it must be authorized by the individual who performed the examination and made the diagnosis.

(e) The laboratory must use acceptable terminology of a recognized system of disease nomenclature in reporting results.

(f) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1274 Standard: Cytology.

(a) *Cytology slide examination site.* All cytology slide preparations must be evaluated on the premises of a laboratory certified to conduct testing in the subspecialty of cytology.

(b) *Staining.* The laboratory must have available and follow written policies and procedures for each of the following, if applicable:

(1) All gynecologic slide preparations must be stained using a Papanicolaou or modified Papanicolaou staining method.

(2) Effective measures to prevent cross-contamination between gynecologic and nongynecologic specimens during the staining process must be used.

(3) Nongynecologic specimens that have a high potential for cross-contamination must be stained separately from other nongynecologic specimens, and the stains must be filtered or changed following staining.

(c) *Control procedures.* The laboratory must establish and follow written policies and procedures for a program designed to detect errors in the performance of cytologic examinations and the reporting of results. The program must include the following:

(1) A review of slides from at least 10 percent of the gynecologic cases interpreted by individuals qualified under §§ 493.1469 or 493.1483, to be negative for epithelial cell abnormalities and other malignant neoplasms (as defined in paragraph (e)(1) of this section).

(i) The review must be performed by an individual who meets one of the following qualifications:

(A) A technical supervisor qualified under §§ 493.1449(b) or (k).

(B) A cytology general supervisor qualified under § 493.1469.

(C) A cytotechnologist qualified under § 493.1483 who has the experience specified in § 493.1469(b)(2).

(ii) Cases must be randomly selected from the total caseload and include negatives and those from patients or groups of patients that are identified as having a higher than average probability of developing cervical cancer based on available patient information.

(iii) The review of those cases selected must be completed before reporting patient results.

(2) Laboratory comparison of clinical information, when available, with cytology reports and comparison of all gynecologic cytology reports with a diagnosis of high-grade squamous intraepithelial lesion (HSIL), adenocarcinoma, or other malignant neoplasms with the histopathology report, if available in the laboratory (either on-site or in storage), and determination of the causes of any discrepancies.

(3) For each patient with a current HSIL, adenocarcinoma, or other malignant neoplasm, laboratory review of all normal or negative gynecologic specimens received within the previous 5 years, if available in the laboratory (either on-site or in storage). If significant discrepancies are found that will affect current patient care, the laboratory must notify the patient's physician and issue an amended report.

(4) Records of initial examinations and all rescreening results must be documented.

(5) An annual statistical laboratory evaluation of the number of—

(i) Cytology cases examined;

(ii) Specimens processed by specimen type;

(iii) Patient cases reported by diagnosis (including the number reported as unsatisfactory for diagnostic interpretation);

(iv) Gynecologic cases with a diagnosis of HSIL, adenocarcinoma, or other malignant neoplasm for which histology results were available for comparison;

(v) Gynecologic cases where cytology and histology are discrepant; and

(vi) Gynecologic cases where any rescreen of a normal or negative specimen results in reclassification as low-grade squamous intraepithelial lesion (LSIL), HSIL, adenocarcinoma, or other malignant neoplasms.

(6) An evaluation of the case reviews of each individual examining slides against the laboratory's overall statistical values, documentation of any discrepancies, including reasons for the deviation and, if appropriate, corrective actions taken.

(d) *Workload limits.* The laboratory must establish and follow written policies and procedures that ensure the following:

(1) The technical supervisor establishes a maximum workload limit for each individual who performs primary screening.

(i) The workload limit is based on the individual's performance using evaluations of the following:

(A) Review of 10 percent of the cases interpreted as negative for the conditions defined in paragraph (e)(1) of this section.

(B) Comparison of the individual's interpretation with the technical supervisor's confirmation of patient smears specified in paragraphs (e)(1) and (e)(3) of this section.

(ii) Each individual's workload limit is reassessed at least every 6 months and adjusted when necessary.

(2) The maximum number of slides examined by an individual in each 24-hour period does not exceed 100 slides (one patient specimen per slide; gynecologic, nongynecologic, or both) irrespective of the site or laboratory. This limit represents an absolute maximum number of slides and must not be employed as an individual's performance target. In addition—

(i) The maximum number of 100 slides is examined in no less than an 8-hour workday;

(ii) For the purposes of establishing workload limits for individuals examining slides in less than an 8-hour workday (includes full-time employees with duties other than slide examination and part-time employees), a period of 8 hours is used to prorate the number of slides that may be examined. The formula—

$$\frac{\text{Number of hours examining slides} \times 100}{8}$$

is used to determine maximum slide volume to be examined;

(iii) Nongynecologic slide preparation made using liquid-based slide preparatory techniques that result in cell dispersion over one-half or less of the total available slide may be counted as one-half slide; and

(iv) Technical supervisors who perform primary screening are not required to include tissue pathology slides and previously examined cytology slides (gynecologic and nongynecologic) in the 100 slide workload limit.

(3) The laboratory must maintain records of the total number of slides examined by each individual during

each 24-hour period and the number of hours spent examining slides in the 24-hour period irrespective of the site or laboratory.

(4) Records are available to document the workload limit for each individual.

(e) *Slide examination and reporting.* The laboratory must establish and follow written policies and procedures that ensure the following:

(1) A technical supervisor confirms each gynecologic slide preparation interpreted to exhibit reactive or reparative changes or any of the following epithelial cell abnormalities:

(i) Squamous cell.

(A) Atypical squamous cells of undetermined significance (ASC–US) or cannot exclude HSIL (ASC–H).

(B) LSIL-Human papillomavirus (HPV)/mild dysplasia/cervical intraepithelial neoplasia 1 (CIN 1).

(C) HSIL-moderate and severe dysplasia, carcinoma in situ (CIS)/CIN 2 and CIN 3 or with features suspicious for invasion.

(D) Squamous cell carcinoma.

(ii) Glandular cell.

(A) Atypical cells not otherwise specified (NOS) or specified in comments (endocervical, endometrial, or glandular).

(B) Atypical cells favor neoplastic (endocervical or glandular).

(C) Endocervical adenocarcinoma in situ.

(D) Adenocarcinoma endocervical, adenocarcinoma endometrial, adenocarcinoma extrauterine, and adenocarcinoma NOS.

(iii) Other malignant neoplasms.

(2) The report of gynecologic slide preparations with conditions specified in paragraph (e)(1) of this section must be signed to reflect the technical supervisory review or, if a computer report is generated with signature, it must reflect an electronic signature authorized by the technical supervisor who performed the review.

(3) All nongynecologic preparations are reviewed by a technical supervisor. The report must be signed to reflect technical supervisory review or, if a computer report is generated with signature, it must reflect an electronic signature authorized by the technical supervisor who performed the review.

(4) Unsatisfactory specimens or slide preparations are identified and reported as unsatisfactory.

(5) The report contains narrative descriptive nomenclature for all results.

(6) Corrected reports issued by the laboratory indicate the basis for correction.

(f) *Record and slide retention.* (1) The laboratory must retain all records and slide preparations as specified in § 493.1105.

(2) Slides may be loaned to proficiency testing programs in lieu of maintaining them for the required time period, provided the laboratory receives written acknowledgment of the receipt of slides by the proficiency testing program and maintains the acknowledgment to document the loan of these slides.

(3) Documentation of slides loaned or referred for purposes other than proficiency testing must be maintained.

(4) All slides must be retrievable upon request.

(g) *Automated and semi-automated screening devices.* When performing evaluations using automated and semi-automated screening devices, the laboratory must follow manufacturer's instructions for preanalytic, analytic, and postanalytic phases of testing, as applicable, and meet the applicable requirements of this subpart K.

(h) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1276 Standard: Clinical cytogenetics.

(a) The laboratory must have policies and procedures for ensuring accurate and reliable patient specimen identification during the process of accessioning, cell preparation, photographing or other image reproduction technique, photographic printing, and reporting and storage of results, karyotypes, and photographs.

(b) The laboratory must have records that document the following:

(1) The media used, reactions observed, number of cells counted, number of cells karyotyped, number of chromosomes counted for each metaphase spread, and the quality of the banding.

(2) The resolution is appropriate for the type of tissue or specimen and the type of study required based on the clinical information provided to the laboratory.

(3) An adequate number of karyotypes are prepared for each patient.

(c) Determination of sex must be performed by full chromosome analysis.

(d) The laboratory report must include a summary and interpretation of the observations, number of cells counted and analyzed, and use the International System of Cytogenetic Nomenclature.

(e) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1278 Standard: Histocompatibility.

(a) *General.* The laboratory must meet the following requirements:

(1) An audible alarm system must be used to monitor the storage temperature of specimens (donor and recipient) and reagents. The laboratory must have an emergency plan for alternate storage.

(2) All patient specimens must be easily retrievable.

(3) Reagent typing sera inventory prepared in-house must indicate source, bleeding date and identification number, reagent specificity, and volume remaining.

(4) If the laboratory uses immunologic reagents (for example, antibodies, antibody-coated particles, or complement) to facilitate or enhance the isolation of lymphocytes, or lymphocyte subsets, the efficacy of the methods must be monitored with appropriate quality control procedures.

(5) Participate in at least one national or regional cell exchange program, if available, or develop an exchange system with another laboratory in order to validate interlaboratory reproducibility.

(b) *HLA typing.* The laboratory must do the following:

(1) Use a technique(s) that is established to optimally define, as applicable, HLA Class I and II specificities.

(2) HLA type all potential transplant recipients at a level appropriate to support clinical transplant protocol and donor selection.

(3) HLA type cells from organ donors referred to the laboratory.

(4) Use HLA antigen terminology that conforms to the latest report of the World Health Organization (W.H.O.) Committee on Nomenclature. Potential new antigens not yet approved by this committee must have a designation that cannot be confused with W.H.O. terminology.

(5) Have available and follow written criteria for the following:

(i) The preparation of cells or cellular extracts (for example, solubilized antigens and nucleic acids), as applicable to the HLA typing technique(s) performed.

(ii) Selecting typing reagents, whether prepared in-house or commercially.

(iii) Ensuring that reagents used for typing are adequate to define all HLA–A, B and DR specificities that are officially recognized by the most recent W.H.O. Committee on Nomenclature and for which reagents are readily available.

(iv) The assignment of HLA antigens.

(v) When antigen redefinition and retyping are required.

(6) Check each HLA typing by testing, at a minimum the following:

(i) A positive control material.

(ii) A negative control material in which, if applicable to the technique performed, cell viability at the end of

incubation is sufficient to permit accurate interpretation of results. In assays in which cell viability is not required, the negative control result must be sufficiently different from the positive control result to permit accurate interpretation of results.

(iii) Positive control materials for specific cell types when applicable (that is, T cells, B cells, and monocytes).

(c) *Disease-associated studies.* The laboratory must check each typing for disease-associated HLA antigens using control materials to monitor the test components and each phase of the test system to ensure acceptable performance.

(d) *Antibody Screening.* The laboratory must do the following:

(1) Use a technique(s) that detects HLA-specific antibody with a specificity equivalent or superior to that of the basic complement-dependent microlymphocytotoxicity assay.

(2) Use a method that distinguishes antibodies to HLA Class II antigens from antibodies to Class I antigens to detect antibodies to HLA Class II antigens.

(3) Use a panel that contains all the major HLA specificities and common splits. If the laboratory does not use commercial panels, it must maintain a list of individuals for fresh panel bleeding.

(4) Make a reasonable attempt to have available monthly serum specimens for all potential transplant recipients for periodic antibody screening and crossmatch.

(5) Have available and follow a written policy consistent with clinical transplant protocols for the frequency of screening potential transplant recipient sera for preformed HLA-specific antibodies.

(6) Check each antibody screening by testing, at a minimum the following:

(i) A positive control material containing antibodies of the appropriate isotype for the assay.

(ii) A negative control material.

(7) As applicable, have available and follow written criteria and procedures for antibody identification to the level appropriate to support clinical transplant protocol.

(e) *Crossmatching.* The laboratory must do the following:

(1) Use a technique(s) documented to have increased sensitivity in comparison with the basic complement-dependent microlymphocytotoxicity assay.

(2) Have available and follow written criteria for the following:

(i) Selecting appropriate patient serum samples for crossmatching.

(ii) The preparation of donor cells or cellular extracts (for example, solubilized antigens and nucleic acids), as applicable to the crossmatch technique(s) performed.

(3) Check each crossmatch and compatibility test for HLA Class II antigenic differences using control materials to monitor the test components and each phase of the test system to ensure acceptable performance.

(f) *Transplantation.* Laboratories performing histocompatibility testing for transfusion and transplantation purposes must do the following:

(1) Have available and follow written policies and protocols specifying the histocompatibility testing (that is, HLA typing, antibody screening, compatibility testing and crossmatching) to be performed for each type of cell, tissue or organ to be transfused or transplanted. The laboratory's policies must include, as applicable—

(i) Testing protocols for cadaver donor, living, living-related, and combined organ and tissue transplants;

(ii) Testing protocols for patients at high risk for allograft rejection; and

(iIi) The level of testing required to support clinical transplant protocols (for example, antigen or allele level).

(2) For renal allotransplantation and combined organ and tissue transplants in which a kidney is to be transplanted, have available results of final crossmatches before the kidney is transplanted.

(3) For nonrenal transplantation, if HLA testing and final crossmatches were not performed prospectively because of an emergency situation, the laboratory must document the circumstances, if known, under which the emergency transplant was performed, and records of the transplant must reflect any information provided to the laboratory by the patient's physician.

(g) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1281 Standard: Comparison of test results.

(a) If a laboratory performs the same test using different methodologies or instruments, or performs the same test at multiple testing sites, the laboratory must have a system that twice a year evaluates and defines the relationship between test results using the different methodologies, instruments, or testing sites.

(b) The laboratory must have a system to identify and assess patient test results that appear inconsistent with the following relevant criteria, when available:

(1) Patient age.

(2) Sex.

(3) Diagnosis or pertinent clinical data.

(4) Distribution of patient test results.

(5) Relationship with other test parameters.

(c) The laboratory must document all test result comparison activities.

§ 493.1282 Standard: Corrective actions.

(a) Corrective action policies and procedures must be available and followed as necessary to maintain the laboratory's operation for testing patient specimens in a manner that ensures accurate and reliable patient test results and reports.

(b) The laboratory must document all corrective actions taken, including actions taken when any of the following occur:

(1) Test systems do not meet the laboratory's verified or established performance specifications, as determined in § 493.1253(b), which include but are not limited to—

(i) Equipment or methodologies that perform outside of established operating parameters or performance specifications;

(ii) Patient test values that are outside of the laboratory's reportable range of test results for the test system; and

(iii) When the laboratory determines that the reference intervals (normal values) for a test procedure are inappropriate for the laboratory's patient population.

(2) Results of control or calibration materials, or both, fail to meet the laboratory's established criteria for acceptability. All patient test results obtained in the unacceptable test run and since the last acceptable test run must be evaluated to determine if patient test results have been adversely affected. The laboratory must take the corrective action necessary to ensure the reporting of accurate and reliable patient test results.

(3) The criteria for proper storage of reagents and specimens, as specified under § 493.1252(b), are not met.

§ 493.1283 Standard: Test records.

(a) The laboratory must maintain an information or record system that includes the following:

(1) The positive identification of the specimen.

(2) The date and time of specimen receipt into the laboratory.

(3) The condition and disposition of specimens that do not meet the laboratory's criteria for specimen acceptability.

(4) The records and dates of all specimen testing, including the identity

of the personnel who performed the test(s).

(b) Records of patient testing including, if applicable, instrument printouts, must be retained.

§ 493.1289 Standard: Analytic systems assessment.

(a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the analytic systems specified in §§ 493.1251 through 493.1283.

(b) The analytic systems assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of analytic systems assessment reviews with appropriate staff.

(c) The laboratory must document all analytic systems assessment activities.

Postanalytic Systems

§ 493.1290 Condition: Postanalytic systems.

Each laboratory that performs nonwaived testing must meet the applicable postanalytic systems requirements in § 493.1291 unless HHS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7) that provides equivalent quality testing. The laboratory must monitor and evaluate the overall quality of the postanalytic systems and correct identified problems as specified in § 493.1299 for each specialty and subspecialty of testing performed.

§ 493.1291 Standard: Test report.

(a) The laboratory must have adequate manual or electronic systems in place to ensure test results and other patient-specific data are accurately and reliably sent from the point of data entry (whether interfaced or entered manually) to final report destination, in a timely manner. This includes the following:

(1) Results reported from calculated data.

(2) Results and patient-specific data electronically reported to network or interfaced systems.

(3) Manually transcribed or electronically transmitted results and patient-specific information reported directly or upon receipt from outside referral laboratories, satellite or point-of-care testing locations.

(b) Test report information maintained as part of the patient's chart or medical record must be readily available to the laboratory and to CMS or a CMS agent upon request.

(c) The test report must indicate the following:

(1) For positive patient identification, either the patient's name and identification number, or an unique patient identifier and identification number.

(2) The name and address of the laboratory location where the test was performed.

(3) The test report date.

(4) The test performed.

(5) Specimen source, when appropriate.

(6) The test result and, if applicable, the units of measurement or interpretation, or both.

(7) Any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability.

(d) Pertinent ''reference intervals'' or ''normal'' values, as determined by the laboratory performing the tests, must be available to the authorized person who ordered the tests and, if applicable, the individual responsible for using the test results.

(e) The laboratory must, upon request, make available to clients a list of test methods employed by the laboratory and, as applicable, the performance specifications established or verified as specified in § 493.1253. In addition, information that may affect the interpretation of test results, for example test interferences, must be provided upon request. Pertinent updates on testing information must be provided to clients whenever changes occur that affect the test results or interpretation of test results.

(f) Test results must be released only to authorized persons and, if applicable, the individual responsible for using the test results and the laboratory that initially requested the test.

(g) The laboratory must immediately alert the individual or entity requesting the test and, if applicable, the individual responsible for using the test results when any test result indicates an imminent life-threatening condition, or panic or alert values.

(h) When the laboratory cannot report patient test results within its established time frames, the laboratory must determine, based on the urgency of the patient test(s) requested, the need to notify the appropriate individual(s) of the delayed testing.

(i) If a laboratory refers patient specimens for testing—

(1) The referring laboratory must not revise results or information directly related to the interpretation of results provided by the testing laboratory;

(2) The referring laboratory may permit each testing laboratory to send the test result directly to the authorized person who initially requested the test. The referring laboratory must retain or be able to produce an exact duplicate of each testing laboratory's report; and

(3) The authorized person who orders a test must be notified by the referring laboratory of the name and address of each laboratory location where the test was performed.

(j) All test reports or records of the information on the test reports must be maintained by the laboratory in a manner that permits ready identification and timely accessibility.

(k) When errors in the reported patient test results are detected, the laboratory must do the following:

(1) Promptly notify the authorized person ordering the test and, if applicable, the individual using the test results of reporting errors.

(2) Issue corrected reports promptly to the authorized person ordering the test and, if applicable, the individual using the test results.

(3) Maintain duplicates of the original report, as well as the corrected report.

§ 493.1299 Standard: Postanalytic systems assessment.

(a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess and, when indicated, correct problems identified in the postanalytic systems specified in § 493.1291.

(b) The postanalytic systems assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of postanalytic systems assessment reviews with appropriate staff.

(c) The laboratory must document all postanalytic systems assessment activities.

Subpart M—Personnel for Nonwaived Testing

19. Revise the heading of Subpart M to read as set forth above.

§ 493.1359 [Amended]

20. § 493.1359(b)(2), remove the reference to ''subpart P''.

§ 493.1407 [Amended]

21. In § 493.1407(e)(5), remove the word ''assurance'' and, add in its place, the word ''assessment''.

22. In § 493.1443, paragraph (b) introductory text is republished, and paragraph (b)(3) is revised to read as follows:

§ 493.1443 Standard: Laboratory director qualifications.

* * * * *

(b) The laboratory director must—

* * * * *

(3) Hold an earned doctoral degree in a chemical, physical, biological, or clinical laboratory science from an accredited institution and—

(i) Be certified and continue to be certified by a board approved by HHS; or

(ii) Before February 24, 2003, must have served or be serving as a director of a laboratory performing high complexity testing and must have at least—

(A) Two years of laboratory training or experience, or both; and

(B) Two years of laboratory experience directing or supervising high complexity testing.

* * * * *

§ 493.1445 [Amended]

23. In § 493.1445(e)(5), remove the word ''assurance'' and add, in its place, the word ''assessment''.

§ 493.1451 [Amended]

24. In § 493.1451(c)(4), remove the cross reference to ''§ 493.1257(c)'' and add, in its place, ''§ 493.1274(d) and (e)''.

§ 493.1471 and § 493.1485 [Amended]

25. In §§ 493.1471(b)(2) and 493.1485(a), remove the cross reference to ''§ 493.1257(d)'' and add, in its place, ''§ 493.1274(c)''.

Subpart P—[Reserved]

26. Subpart P consisting of §§ 493.1701 through 493.1721, is removed and reserved.

Subpart R—Enforcement Procedures

§ 493.1844 [Amended]

27. In § 493.1844(c)(1), remove the reference to ''subpart P''.

Subpart T—Consultations

§ 493.2001 [Amended]

28. Amend § 493.2001 as follows:

a. In paragraph (e)(1), remove the words ''tests and examinations of moderate complexity (including the subcategory) and high complexity'' and add, in their place, the words ''nonwaived testing''.

b. Revise paragraph (e)(4) to read as follows:

* * * * *

(e) * * *

(4) Facility administration and quality systems standards.

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Dated: October 7, 2002.

Thomas A. Scully,

Administrator, Centers for Medicare & Medicaid Services.

Dated: December 13, 2002.

Tommy G. Thompson,

Secretary.

[FR Doc. 03–1230 Filed 1–23–03; 8:45 am]

BILLING CODE 4120–01–P